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## PALLADIUM-CATALYZED C–C BOND FORMATION INVOLVING AROMATIC C–H ACTIVATION

### III \*. ASPECTS OF AROMATIC SUBSTITUTION AND STRUCTURE OF 1-BROMO-3-[3-(2-METHYLENECYCLOHEX-5-EN-1-YL)BICYCLO[2.2.1]HEPT-2-YL]-4-BICYCLO[2.2.1]HEPT-2-YLBENZENE \*\*

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### Summary

The palladium-catalyzed reaction of substituted bromobenzenes with bicyclo-[2.2.1]hept-2-ene leads to products derived from the insertion of the latter into the aryl–palladium bond, followed by different types of aromatic C–H activation which imply palladium transfer from bicycloheptane to arene. The isolation of a compound derived from the initial bicycloheptene insertion, transpalladation to the aromatic ring, and further insertion of two bicycloheptene units provides a link between aromatic substitution via palladation and competitive formation of benzocyclobutene derivatives. The latter have also been obtained from the reaction of bromo derivatives and bicycloheptene in a 1/1 molar ratio.

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### Introduction

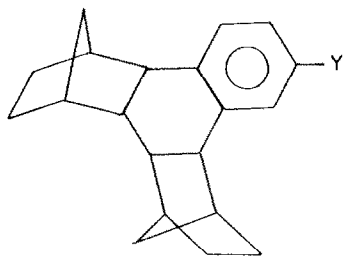
We previously described [1,2] \* two different kinds of C–C bond formation

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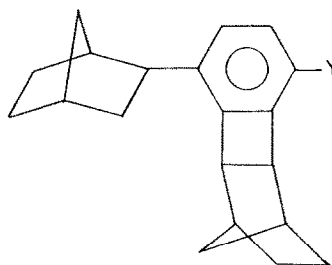
\* Notes I and II, respectively ref. 1 and ref. 2.

\*\* Dedicated to Professor Jack Halpern on the occasion of his 60th birthday.

reactions involving aromatic C–H activation:



(I)



(II)

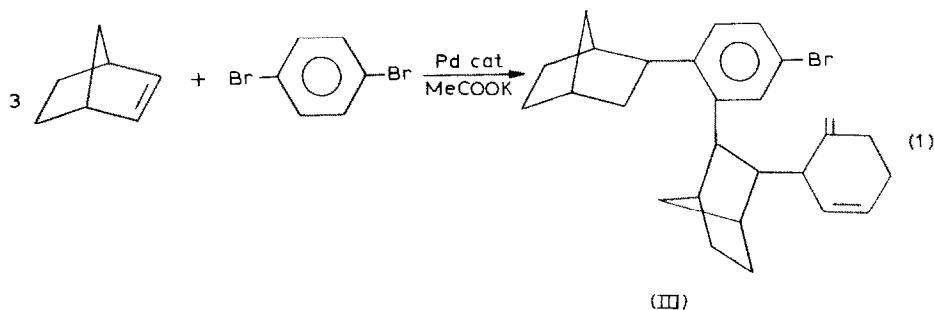
Compound I predominates with  $Y = H, OCH_3$ , whereas compound II prevails when  $Y = NO_2$ .

The formation of I is in accord with an electrophilic palladation reaction, but the pattern leading to II appears to be different.

Investigation of the by-products has led us to identify new classes of compounds, the structures of which could throw light on the course of these reactions. Among the compounds investigated, the one deriving from the reaction of 1,4-dibromobenzene could be prepared in substantial quantities and was studied further.

## Results

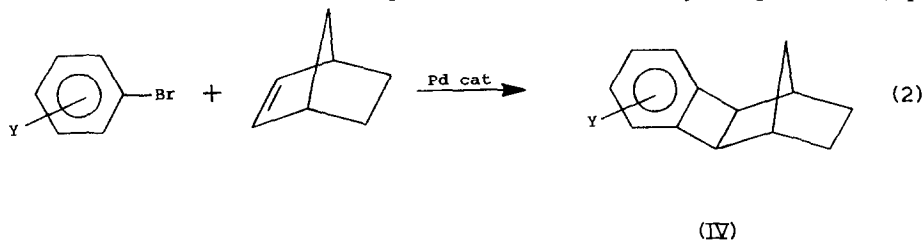
The reaction of 1,4-dibromobenzene with two molecules of bicyclo[2.2.1]hept-2-ene and one molecule of potassium acetate in the presence of  $Pd(PPh_3)_4$  at  $105^\circ C$  in anisole leads to compounds I and II ( $Y = Br$ ) in comparable amounts and to other compounds resulting from the reaction of two and three molecules of bicycloheptene with dibromobenzene, with final ring-opening, as shown by the presence of two exocyclic and two ring vinylic protons in the NMR spectrum. Compounds I, II ( $Y = Br$ ) and III were isolated by column chromatography. Compounds I and II ( $Y = Br$ ) show structures of the type reported previously [1,2]. Compound III, which contains three bicycloheptene molecules, consisted of two diastereoisomers approximately in a 1/1 ratio as shown by the double NMR signals for the benzylic protons at  $\delta$  3.13, 3.06 and 2.90, 2.74 ppm. One of the two diastereoisomers was caused to crystallize from *n*-hexane at  $0^\circ C$  as a white solid, m.p.  $166\text{--}167^\circ C$ . The structure of compound III was determined by X-ray method. Its formation corresponds to eq. 1:



(III)

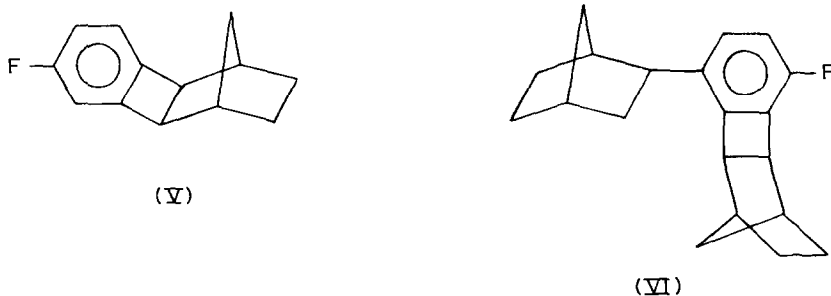
As mentioned before, the reaction is not limited to 1,4-dibromobenzene. It always competes with the reaction leading to benzocyclobutene-derived structures of type II, depending on the type of substituent in the aromatic ring. More electronegative substituents such as  $\text{NO}_2$  tend to shift the reaction towards the formation of type II compounds.

To ascertain whether benzocyclobutene derivatives of type IV could be formed from aromatic bromides, without previous insertion of a bicycloheptene unit (eq. 2):



we investigated the by-products of the 1,4-dibromobenzene reaction ( $Y = p\text{-Br}$ ) carefully and found only traces of IV with Y in the *meta* position to the cyclobutene junction. This compound was identical to that reported [3]. From the reaction of 1,3-dibromobenzene, small amounts of the same compound were obtained.

With  $p\text{-NO}_2$  or  $p\text{-F}$  as the substituent, compound IV also formed to a limited extent. For example, 1-bromo-4-fluorobenzene gave V and VI in 5 and 19% yield, respectively:



Under the same conditions but without the palladium catalyst, this reaction was not observed.

The formation of compound IV was accompanied with insertion reactions of one or more bicycloheptene units into the aryl-Pd bond according to previously reported patterns [1,4,5].

### Molecular structure of III \*

A perspective view of the molecule, together with the atomic numbering scheme adopted, is given in Fig. 1.

\* The atomic coordinates are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW, Great Britain. Any requests should be accompanied with a full literature citation. Tables of observed and calculated structure factors and of thermal parameters are available on request from one of the authors (G.B.).

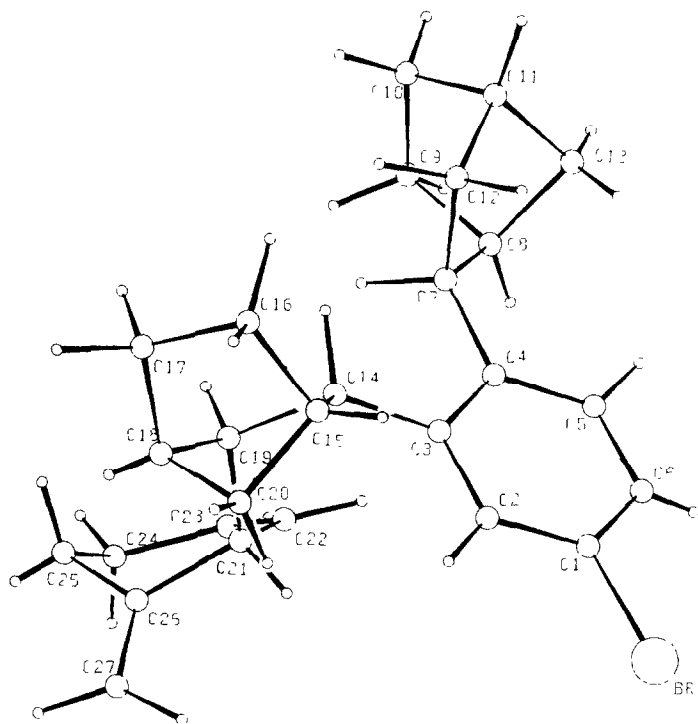


Fig. 1. Perspective view of the molecule of III.

The aromatic ring is planar and the mean bond lengths and internal angles are standard within the errors (1.395(4) Å, 119.9(6)°). The bromine atom is out-of-plane by 0.071 Å and, in accordance with the effects of substituents on the aromatic ring skeleton [6], the internal angle at Br is larger (121.5(3)°) than the adjacent ones (119.8(3), 118.5(4)°).

The geometry of the bicycloheptane groups is normal and their  $Csp^3-Csp^3$  bond lengths range from 1.516(5) to 1.595(4) Å (mean 1.544(5) Å). This value is rather larger than the expected value of 1.537(5) Å proposed by Sutton [7].

As always observed in bicycloheptane derivatives, the endocyclic angles at C(13) and C(20) are noticeably smaller (95.0(3), 94.1(3)°) than the others of the bicycloheptane molecule.

The cyclohexenic ring is almost a half-chair conformation. Following the Cremer and Pople notation [8], the ring puckering parameters are  $Q$  0.48 Å,  $\phi$  93.6° and  $\theta$  40.6°. These values are similar to the values of  $Q$  0.38 Å,  $\phi$  90° and  $\theta$  50.7° [9] calculated for the half-chair conformation.

The molecules are joined in the crystal mostly by Van der Waals interactions. The Br...H(21) distance ( $-x, -y, -z$ ) of 3.04(3) Å is shorter than the sum of the Van der Waals radii.

## Discussion

Together with the previous ones, the results obtained show that the reaction leading to aromatic C–H activation is subject to subtle influence by substituents.

The formation of compound III is significant because our earlier observations had shown that the bicycloheptyl–Pd bond could insert another molecule of bicycloheptene in a sort of initial polymerization [5]. That the chain could be interrupted at the level of the first bicycloheptene unit and continue from the aryl nucleus is a new aspect which has no precedent in the literature. This behaviour must involve a transmetallation reaction because the only source of the palladium(II) complex able to effect the known direct palladation of the aromatic nucleus [10] derives from the oxidative addition of bromo derivative to palladium(0) followed by bicycloheptene insertion. One should therefore postulate the sequence shown in the general Scheme 1 (PPh<sub>3</sub> is omitted for simplicity). All bicycloheptene insertions are *cis, exo*.

Whereas the tendency to form a four-membered ring is rather strong in the presence of a nitro group, with the less electron-withdrawing bromide substituent the aryl-palladium bond gives both compounds I and II (Y = Br) in comparable amounts and compound III, the presence of which indicates a preference of the system to proceed further with bicycloheptene insertion rather than undergoing ring closure. We are thus led to believe that, in general, when an aryl-palladium bond is formed there must be competition between the four-membered ring closure (involving H-abstraction from the aromatic ring) and double-bond insertion.

If this were the case, we should observe the same competition at the level of the first oxidative addition of the aromatic halide to palladium. Experiments with simple bromo derivatives showed that the four-membered ring closure can be induced at the level of the first Pd–C bond formed. The reaction could involve either aryne [11] or, more likely, palladacycle formation by oxidative addition to aromatic C–H.

The benzocyclobutene-forming reactions thus appear to compete with direct aromatic substitution both at the stage of the first oxidative addition of the aromatic halide to palladium and at the stage of the transmetallation leading either to compound II or III.

## Experimental

All reagents were commercial products, and were used without further purification. Pd(PPh<sub>3</sub>)<sub>4</sub> was prepared according to ref. 12. All reactions were carried out under nitrogen. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on Varian EM-360, XL-100 and Bruker CXP-200 instruments in CDCl<sub>3</sub>, with TMS as internal standard. Mass spectra were recorded with a Finnigan 1020 instrument at 70 eV.

### *Reaction of 1,4-dibromobenzene with bicyclo[2.2.1]hept-2-ene*

A mixture of Pd(PPh<sub>3</sub>)<sub>4</sub> (162 mg, 0.14 mmol), bicyclo[2.2.1]hept-2-ene (507 mg, 5.4 mmol), 1,4-dibromobenzene (637 mg, 2.7 mmol) and anhydrous potassium acetate (265 mg, 2.7 mmol) in dry and degassed anisole (5 ml) was heated at 105 °C under nitrogen in a Schlenk-type flask containing a magnetic stirring bar. The conversion of 1,4-dibromobenzene was 83% in 24 h. After conventional treatment, the products were separated by chromatography on a SiO<sub>2</sub> column, using hexane as the eluent. The following quantities were eluted: 108 mg dibromobenzene, 17%; 203

mg I (Y = Br), 22%; 194 mg II (Y = Br), 21%; 94 mg III, 8%; and 65 mg ( $M^+$  344, 342, not fully characterized), 7%. Traces of IV, with Y *meta* to the cyclobutene junction [3], were also obtained.

I (Y = Br), mass spectrum:  $M^+$  344, 342,  $m/e$  277, 276, 275, 274, 221, 219, 209.

SCHEME 1

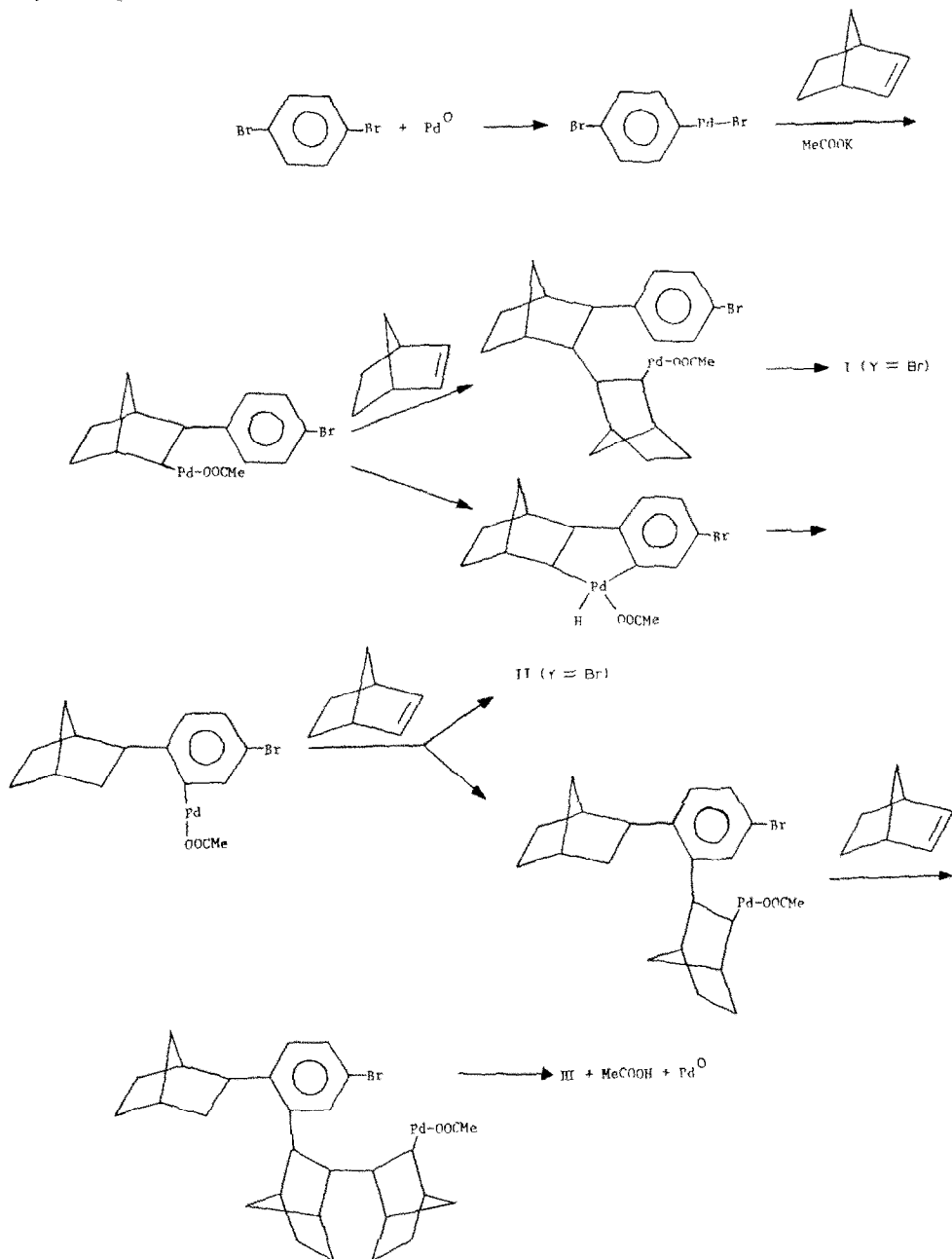


TABLE 1  
CRYSTAL DATA AND EXPERIMENTAL DETAILS

Formula	C <sub>27</sub> H <sub>33</sub> Br	Space group	$P\bar{1}$
$a$ (Å)	11.470(3)	Radiation	Cu- $K_{\alpha}$
$b$	10.407(2)	$\lambda$ (Å)	1.5418
$c$	10.268(2)	Number ind. refl.	3897
$\alpha$ (°)	105.82(3)	Number obs. refl. ( $> 2\sigma$ )	3510
$\beta$	68.21(2)	$\theta$ range (°)	3–70
$\gamma$	98.98(3)	Final $R$	0.050
$V$ (Å <sup>3</sup> )	1092.9	Final $R_w$	0.069
$M$	437.5	$w = k(\sigma^2 F + gF)$	$k = 2.5636$ $g = 0.0509$
$Z$	2	$(\Delta\rho)_{\max}$ (eÅ <sup>3</sup> )	0.51
$D_c$ (g cm <sup>-3</sup> )	1.33		
$F(000)$	460		
$\mu$ (cm <sup>-1</sup> )	26.12		

208, 207, 206, 196, 195, 165, 154, 153, 152, 141, 128, 127, 115, 81, 67; <sup>1</sup>H NMR (60 MHz):  $\delta$  7.4–6.9 (m, 3H), 2.75 (br d,  $J$  8 Hz, 2H), 2.15 (m, 2H), 2.05 (m, 2H), 1.9–0.8 (14H) ppm; <sup>13</sup>C NMR (25.2 MHz):  $\delta$  140.6, 137.2, 131.7, 130.9, 128.0, 118.6, 47.8, 47.6, 46.2, 45.4, 45.1, 33.4, 30.5, 28.8 ppm.

II (Y = Br), mass spectrum:  $M^+$  344, 342,  $m/e$  303, 301, 223, 221, 183, 179, 178, 165, 154, 153, 152, 141, 128, 115, 95, 79, 67, 55; <sup>1</sup>H NMR (200 MHz):  $\delta$  7.10 (d,  $J$  8 Hz, 1H), 6.90 (d,  $J$  8 Hz, 1H), 3.16 (d,  $J$  4 Hz, 1H), 3.10 (d,  $J$  4 Hz, 1H), 2.64 (dd,  $J$  6 and 8 Hz, 1H), 2.42 (m, 1H), 2.32 (m, 3H), 1.9–1.1 (12H), 1.00 (br d,  $J$  10 Hz, 1H), 0.86 (br d,  $J$  10 Hz, 1H) ppm. <sup>13</sup>C NMR (25.2 MHz): the same pattern was observed for II (Y = NO<sub>2</sub>), the crystal structure of which has been reported [2]:  $\delta$  145.6, 145.2, 141.0, 129.7, 126.8, 111.7, 49.7, 49.4, 43.5, 42.7, 36.7, 36.5, 36.2, 36.0, 35.0, 32.0, 30.2, 28.8, 27.8, 27.6 ppm.

III, mass spectrum:  $M^+$  438, 436,  $m/e$  345, 343, 263, 185, 182, 165, 153, 152, 141, 128, 114, 96, 93, 91, 77, 67, 65, 55; <sup>1</sup>H NMR (200 MHz):  $\delta$  7.46 (d,  $J$  2 Hz, 1H), 7.25 (dd,  $J$  2 and 8 Hz, 1H), 7.11 (d,  $J$  8 Hz, 1H), 5.35 (br d,  $J$  9.5 Hz, 1H), 4.73 (br s, 1H), 4.58 (d,  $J$  2.2 Hz, 1H), 4.66–4.52 (1H), 3.06 (d,  $J$  9 Hz, 1H), 2.74 (dd,  $J$  6 and 8 Hz, 1H), 2.47 (br s, 1H), 2.4–1.1 (23H) ppm.

#### Reaction of 1-bromo-4-fluorobenzene with bicyclo[2.2.1]hept-2-ene

A mixture of Pd(PPh<sub>3</sub>)<sub>4</sub> (245 mg, 0.21 mmol), bicyclo[2.2.1]hept-2-ene (200 mg, 2.1 mmol), 1-bromo-4-fluorobenzene (367 mg, 2.1 mmol) and anhydrous potassium acetate (206 mg, 2.1 mmol) in dry and degassed anisole (4 ml) was heated at 105 °C under nitrogen for 24 h in a Schlenk-type flask containing a magnetic stirring bar. Products V and VI were obtained in 5 and 19% yield, respectively (determined by GLC). Products formed by the reactions of one or more molecules of bicycloheptene with 1-bromo-4-fluorobenzene, according to already described patterns [1,4,5], were also present.

V, mass spectrum:  $M^+$  188,  $m/e$  160, 159, 148, 147, 146, 134, 133, 127, 120, 107, 83, 79, 63, 55, 51; <sup>1</sup>H NMR (200 MHz):  $\delta$  6.95–6.75 (m, 2H), 6.68 (dd,  $J$  8 and 2 Hz, 1H), 3.11 (br s, 2H), 2.24 (br s, 2H), 1.67–1.50 (m, 2H), 1.23–1.08 (m, 2H), 0.96 (d quintets,  $J$  10.5 and 1.5 Hz, 1H), 0.82 (d quintets,  $J$  10.5 and 2.0 Hz, 1H) ppm. <sup>13</sup>C NMR (25.2 MHz):  $\delta$  162.7 (d,  $J$ (C,F) 243.2 Hz), 147.4 (d,  $J$ (C,F) 6.0 Hz), 141.3 (d,

$J(\text{C,F})$  2.1 Hz), 123.1 (d,  $J(\text{C,F})$  8.6 Hz), 114.2 (d,  $J(\text{C,F})$  23.4 Hz), 109.5 (d,  $J(\text{C,F})$  21.5 Hz), 49.5 (d), 36.7 (d), 36.4 (d), 31.8 (t), 27.7 (t) ppm.

VI, mass spectrum. The pattern was similar to that observed for compounds II:  $M^+$  282,  $m/e$  241, 183, 173, 171, 170, 161, 159, 146, 145, 133, 95, 79, 67, 55.

#### *Structure determination*

A prismatic crystal of  $0.21 \times 0.33 \times 0.56$  mm was used for data collection at room temperature on a Siemens AED single crystal diffractometer equipped with a General Automation Jumbo 220 computer. Intensity data were measured using a modified version [13] of the Lehmann and Larsen [14] procedure. A check reflection measured every 50 counts did not show variation during the data collection time. All the data were corrected for Lorentz and polarisation effects while those for absorption were ignored. Crystal data and experimental details are reported in Table 1.

The structure was solved by direct methods with the SHELX program [15]. The heavy atoms were refined by block-matrix least-squares with anisotropic thermal parameters, while the hydrogen atoms, found in a  $\Delta F$  map, were refined isotropically.

All the calculations were performed on a GOULD-SEL 32/77 computer.

#### **Acknowledgement**

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