# Synthesis and NMR Characterization of a Dioxa-Analog of Benzo[*a*]pyrene: the 1-Benzopyrano[6,5,4-*mna*]-xanthene (1,6-Dioxabenzo[*a*]pyrene) †



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1,6-Dioxabenzo[*a*]pyrene, the first dioxa-analog of benzo[*a*]pyrene, was synthesized from 5-methoxy-1-naphthol in an eight-step reaction involving two *peri*-heterocyclizations.

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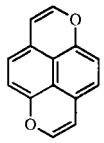
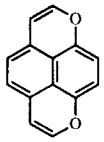
We have recently reported [1,2] the synthesis of 1,6- and 1,8-dioxapyrenes. These two heterocyclic skeletons showed an unexpected disruption of the π electrons extended delocalization, and a marked ethylenic character of their heterocyclic double bonds [2,3]. A photobiological study indicated that 1,6-dioxapyrene (**1**) is a potent photosensitizer generating singlet oxygen and inducing oxidative damage to cellular DNA [4]. The 1,8-dioxapyrene (**2**) exhibits the same $^1O_2$ quantum yield but a sevenfold higher biological activity [5].



1



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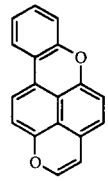

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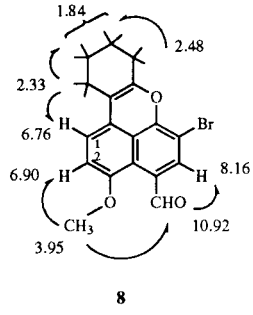
In the frame of our work concerning the dioxa-analog of polycyclic aromatic hydrocarbons, these results prompted us to synthesize the 1,6-dioxa-analog **3** of benzo[*a*]pyrene with the aim of comparing its physicochemical, photobiological and genotoxic properties with those of the benzo[*a*]pyrene itself. We describe herein the synthesis and some spectroscopic data of compound **3**.

Chemistry.

Starting from the already known 5-methoxy-1-naphthol (**4**) [6], the reaction process involved eight stages, affording the end product **3** in an overall yield of 5.5% (Scheme 1). As the position 2 of the naphthalene ring of **4** is the most reactive one towards electrophilic cyclizations, inducing an "undesirable" (*ortho*) regioselectivity, we had to protect it until the first annelation was achieved. Otherwise, a naphthofuran derivative **17** was the only product obtained after cyclization of the ether **16** either with tinIV chloride or in strong acidic medium (Scheme 2).

The required protection of the position 2 of the naphthol **4** was achieved by its transformation into the 2-bromo derivative **5** [7], whose bromine atom was removed in a further step. The bromo ketoether **6** was then *peri*-cyclized by tinIV chloride, furnishing the annelated tetrahydrobenzoxanthene **7** in a better yield than those obtainable in strong acidic medium.

Due to the presence of the bromine atom, which excludes a metalation reaction to obtain a *peri* aldehyde (relative to the methoxy group) of **7**, we had to use an electrophilic formylation. Unfortunately, this reaction led to a mixture of two isomers formylated in the *peri* (compound **8**, 40%) and at the position 1, *meta* with respect to the methoxy (compound **9**, 46%). The nmr analysis (Figure 1) shows the assignments of the $^1H$ signals (δ ppm) and the observed nuclear Overhauser effects (arrows) for compounds **8** and **9**. The position of the formyl group is thus established for the aldehyde **9**.

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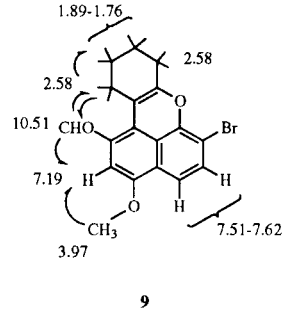
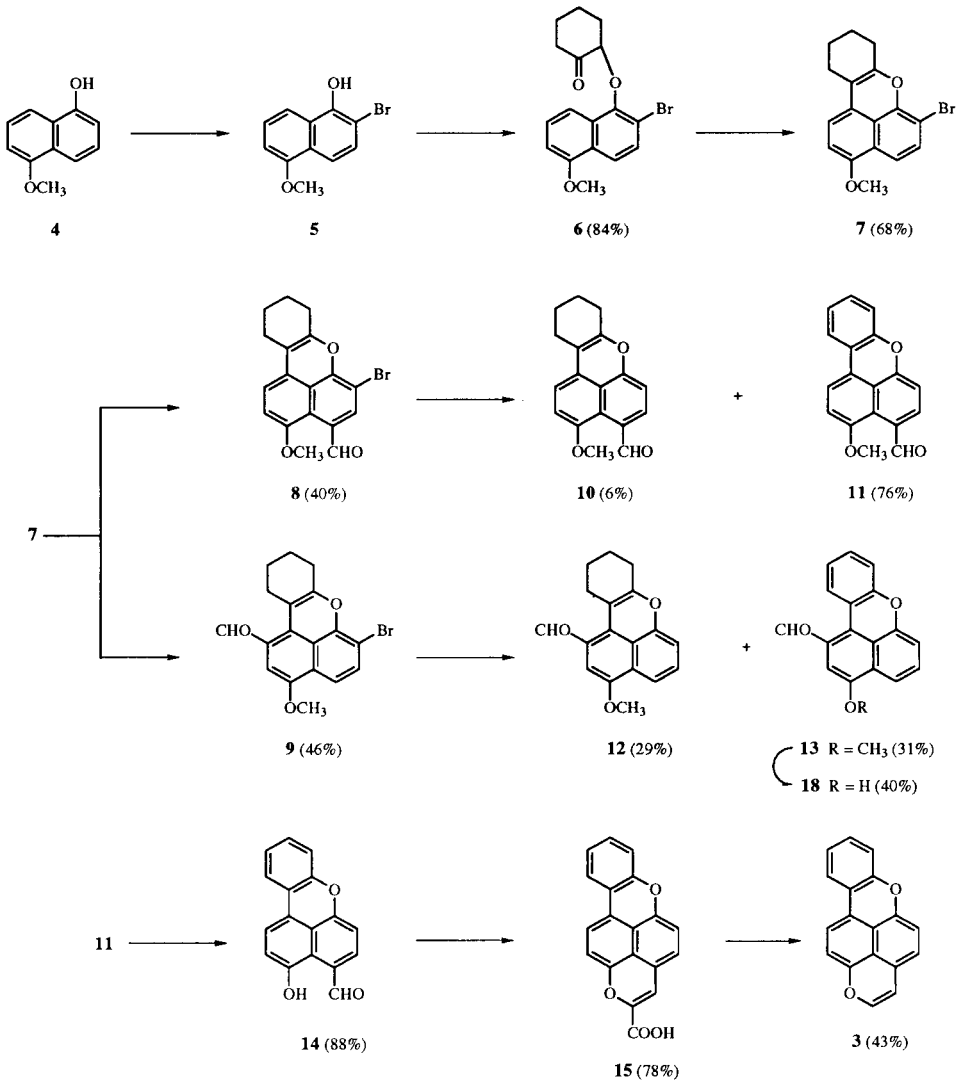



9

Figure 1. $^1H$ nmr data of aldehydes **8** and **9**.

The structure was unambiguously confirmed by an X-ray analysis (*cf.* experimental) of the debrominated aldehyde **12** (Figure 2).

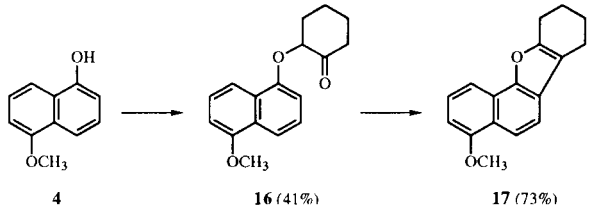
Scheme 1




The unexpected formylation of **7** at the *meta* position relative to the methoxy group, probably reflects both a steric hindrance at position 2 (due to the orientation of the methoxy group) and an unusual electronic arrangement of the tetrahydrobenzoxanthene skeleton, probably due to the conjugation of the heterocyclic double bond.

Nevertheless, the separation of the two aldehydes **8** and **9** was easily achieved by column chromatography, furnishing the *peri*-aldehyde required for the second annelation. The removal of the bromine atom of aldehyde **8** by the caproic acid-copper powder method [8] directly led to the dehydrogenated formylmethoxybenzoxanthene **11** as the major product (76%) along with a small quantity of the tetrahydroaldehyde **10** (6%). In contrast, the removal of bromine of the aldehyde **9** using the same reagents and conditions, led to equal quantities of the tetrahydro **12** and aromatized **13** aldehydes.

Scheme 2




The demethylation of the *peri* methoxylated aldehyde **11** was achieved by aluminum chloride which very slowly (100 hours) led to the hydroxylated aldehyde **14** further annelated in the usual way, affording the acid **15**. The decarboxylation of **15** furnished the 1,6-dioxabenzo-[*a*]pyrene **3** which, as expected if considering the results of our previous works [1-3] exhibits less aromatic character than benzo[*a*]pyrene itself as illustrated by $^{1}H$-$^{13}C$

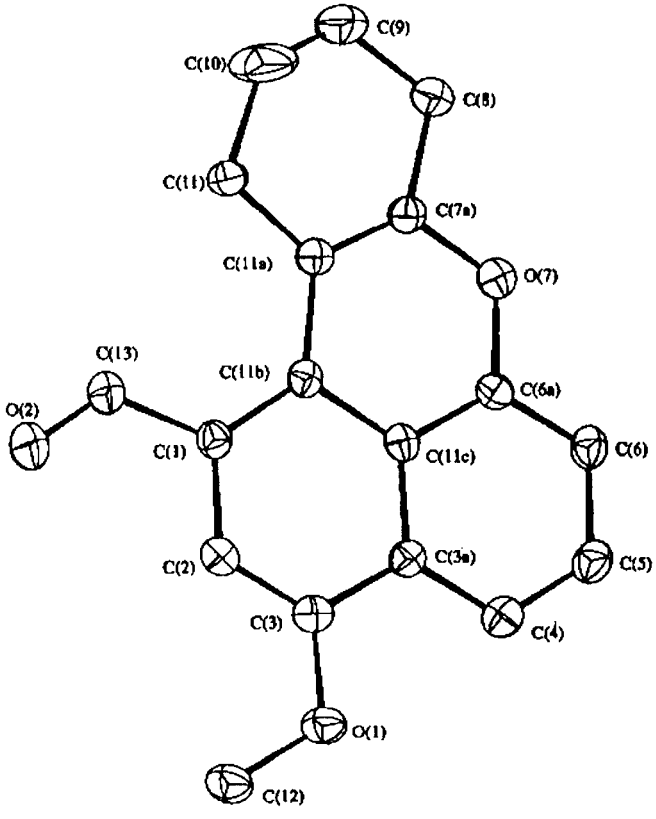



Figure 2. Cameron view of compound **12**.

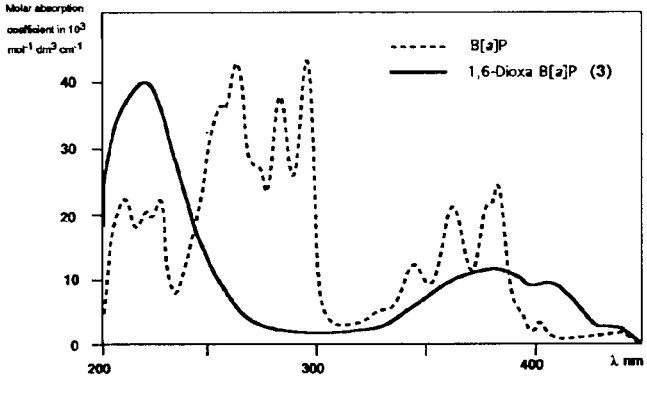



Figure 3. The uv spectra of **3** and B[*a*]P, in ethanol.

nmr (detailed below) and uv-spectroscopy (Figure 3).

NMR Analysis.

1) Assignments of the $^1$H Spectra of **3**.

The assignment of the $^1$H signals was straightforward. The four protons of ring A show the expected *ortho* and *meta* coupling interactions. Among them, H-7 was identified due to the shielding effect of the *ortho* oxygen atom O-6 and H-10 due to the deshielding effect of ring B.

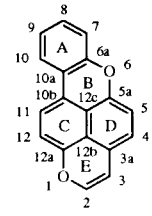
Decoupling experiments lead to the assignment of H-8 and H-9. The other protons give AX or AB systems. The coupling constant between the two more shielded signals, 5.9 Hz, is significantly less than the *ortho* coupling constants (*circa* 8 Hz). They were assigned to the protons of ring E, the most shielded corresponding to H-3. Upon saturation of this proton, nuclear Overhauser effects were observed for H-2 and H-4. Finally, H-11 undergoes the deshielding effect of ring A and selective irradiation of this proton allows the assignment of H-12 which is thus distinguished from the proximate H-5. The data are given in Table 1.

2) Assignments of the $^{13}$C Spectra of **3**.

Univocal assignments of the $^{13}$C signals would be impossible on the basis of chemical shifts. They were obtained by use of inverse δ $^{13}$C-δ $^1$H 2D correlations through $^1$J (HMQC) [9] and $^n$J (HMBC) [10] interactions. Figure 4 shows, in particular, the correlations detected for the non-protonated carbons at the frequency of each proton in an experiment optimised for $^n$J = 7 Hz.

Table 1

$^1$H and $^{13}$C NMR Data for **3**. δ ppm with Respect to Internal TMS (0.02 *M* solution for $^1$H spectrum and 0.3 *M* for $^{13}$C spectrum, in $CDCl_3$)




| Atom | δ $^1$H | δ $^{13}$C | η ($^{13}$C) [a] | $T_1$ (s) [a] | $T_1$ (s) [b] |
|---|---|---|---|---|---|
| 2* | 6.33 | 143.1 | 1.5 | 1.9 | 2.0 |
| 3 | 5.61 | 107.6 | 1.5 | 2.1 | 2.1 |
| 3a | | 122.0 | 0.3 | 6.3 | 10 |
| 4* | 6.37 | 116.9 | 1.5 | 2.1 | 2.2 |
| 5* | 6.41 | 108.9 | 1.4 | 2.5 | 2.3 |
| 5a | | 149.4 | 0.2 | 9.3 | 14 |
| 6a | | 152.5 | 0.3 | 14 | 24 |
| 7 | 6.79 | 116.9 | 1.5 | 2.6 | 2.5 |
| 8 | 7.07 | 129.1 | 1.6 | 1.9 | 1.9 |
| 9 | 6.93 | 123.5 | 1.5 | 2.0 | 2.0 |
| 10 | 7.45 | 121.8 | 1.6 | 2.5 | 2.4 |
| 10a | | 121.5 | 0.2 | 13 | 25 |
| 10b | | 120.0 | 0.2 | 6.3 | 10 |
| 11 | 7.16 | 116.8 | 1.5 | 2.1 | 2.3 |
| 12* | 6.41 | 108.7 | 1.6 | 2.5 | 2.3 |
| 12a | | 152.5 | 0.3 | 14 | 24 |
| 12b | | 126.3 | 0.2 | 13 | 28 |
| 12c | | 124.1 | 0.2 | 14 | 28 |

[a] η, $T_1$ measured at 125.13 MHz. [b] η, $T_1$ measured at 75.13 MHz. *H-2, H-4, H-12 and H-5 gave separate signals at respectively 6.29, 6.31, 6.34 and 6.36 ppm for the 0.3*M* solution used in the 2D $^{13}$C-$^1$H experiments.

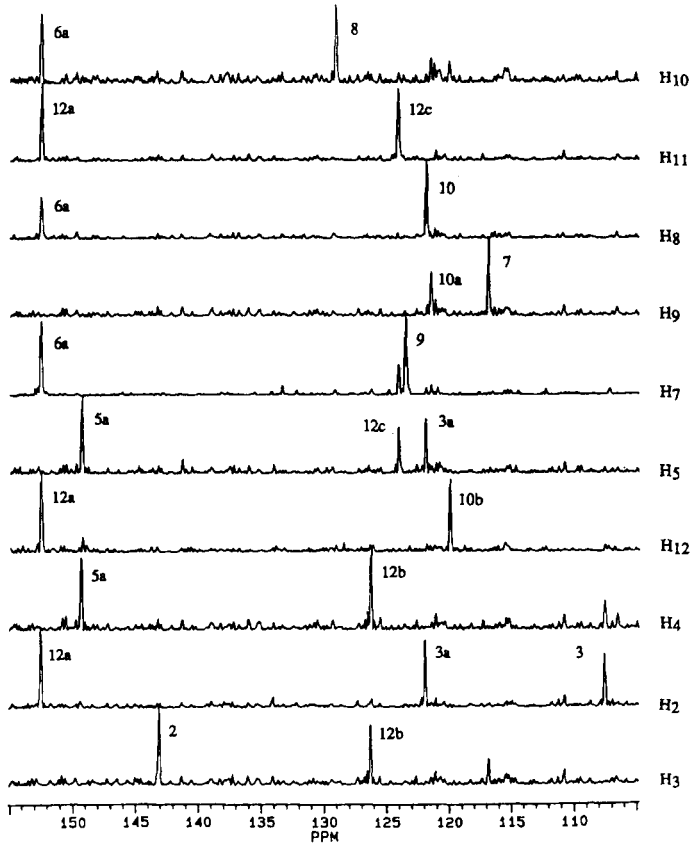



Figure 4. Inverse δ $^{13}$C-δ $^{1}$H 2D correlations of **3**.

Relaxation time $T_1$ and nuclear Overhauser effects η were also measured for the $^{13}$C atoms. The data are collected in Table 1.

3) Discussion.

Compared to the carbons situated at the same positions in 1,6-dioxapyrene [3], the $^{13}$C nuclei of **3** undergo only minor shifts. For ring A, it is interesting to compare **3** and benzo[*a*]pyrene [11]. The chemical shifts of the carbons show moderate electron release from the oxygen atoms except at C-7 (Δδ-11.9 ppm) situated in *ortho* position with respect to 0-6. C-8 is deshielded by 3.2 ppm. As a consequence, the protons in **3** (except H-11) are only weakly deshielded with respect to their analogs in 1,6-dioxapyrene. The proton H-11 is deshielded by 1 ppm with respect to 1,6-dioxapyrene and, contrarily, is shielded by 1.8 ppm with respect to benzo[*a*]pyrene [12]. The first effect might result essentially from the ring current anisotropy of ring A and the second one from the lack of extended delocalization of π electrons over all the molecule. This hypothesis is well supported by considering the protons in ring A. Compared to that of benzo[*a*]pyrene, the shieldings are respectively -1.3, -0.6, -0.8, -1.5 ppm for H-7, H-8, H-9 and H-10. Thus, the disruption of extended delocalization of π electrons which characterized 1,6- or 1,8-dioxapyrene is also well demonstrated for 1,6-dioxabenzo[*a*]pyrene.

The nuclear Overhauser effects (NOE) were measured for all the carbons at 125.13 MHz using a carefully degassed sample. The η values are *circa* 1.5 for the protonated carbons, less than the theoretical value of 2, and circa 0.2 only for the non-protonated carbons. Several mechanisms must be involved in longitudinal relaxation besides the dipolar mechanism which is important for the protonated carbons but plays a minor role for the non-protonated carbons.

The relaxation times $T_1$ were measured at two frequencies, 125.13 MHz and 75.13 MHz. The significant increase of the $T_1$ measured for the non-protonated carbons when the frequency is lowered shows that relaxation due to chemical shift anisotropy is especially important in this molecule. Considering the moderate size of the molecule, it is not possible to disregard relaxation due to spin rotation.

Finally, differences in the relaxation times of the non-protonated carbons show some anisotropy in the overall reorientation motion of the molecule.

Table 2

Experimental Data for the Crystallographic Analysis

| | |
|---|---|
| Molecular formula | $C_{18}H_{16}O_3$ |
| Molecular weight | 280.32 |
| Crystal system | Monoclinic |
| Space group | p 21/c |
| a, Å | 7.894(3) |
| b, Å | 18.204(4) |
| c, Å | 9.400 (1) |
| β, deg. | 91.24(2) |
| V, Å$^3$ | 1350(1) |
| Z | 4 |
| ρ calc., g. cm$^{-3}$ | 1.38 |
| F(000) | 592 |
| μ, cm$^{-1}$ | 18.1 |
| Temperature, °C | 18 |
| Crystal size, mm | 0.75 0.30 0.25 |
| Scan type | ω–2θ |
| Scan width | 0.8 + 0.34 tan |
| θ range, deg. | 1-25 |
| Standard reflections | Two, measured every two hours |
| Nb of measured reflections | 2379 |
| Nb of reflections used I ≥ 36 (I) | 1142 |
| Min-max height in final Δρ, e.Å$^{-3}$ | -0.30-0.26 |
| Nb of refined parameters | 191 |
| R = [Σ (ΔF)/ΣF$_o$] | 0.063 |
| R$_w$ = Σ$_w$(ΔF)2/ΣF$_o^{2\ 1/2}$ | 0.063 |
| w = 1 | |

Table 3

Fractional Atomic Coordinates for Non-hydrogen Atoms of **12**

| Atom | x/a | y/b | z/c | U(eqv) |
|---|---|---|---|---|
| 0(1) | 0.4508(5) | 0.3754(2) | 0.7714(4) | 0.0646 |
| 0(2) | 0.2639(6) | 0.6348(2) | 0.8172(4) | 0.0823 |
| 0(7) | 0.1501(5) | 0.4744(2) | 0.2130(4) | 0.0636 |
| C(l) | 0.2653(7) | 0.5491(3) | 0.6304(5) | 0.0500 |
| C(2) | 0.3423(7) | 0.4977(3) | 0.7258(5) | 0.0510 |
| C(3) | 0.3808(7) | 0.4284(3) | 0.6846(6) | 0.0506 |
| C(4) | 0.3770(7) | 0.3325(3) | 0.5005(6) | 0.0589 |
| C(5) | 0.3353(8) | 0.3105(3) | 0.3633(6) | 0.0625 |
| C(6) | 0.2583(8) | 0.3591(3) | 0.2672(6) | 0.0584 |
| C(8) | 0.0464(8) | 0.5855(3) | 0.1205(6) | 0.0663 |
| C(9) | 0.0120(1) | 0.6630(5) | 0.1484(8) | 0.1050 |
| C(10) | 0.0770(2) | 0.6943(4) | 0.2610(1) | 0.1147 |
| C(11) | 0.1210(7) | 0.6567(3) | 0.3951(6) | 0.0568 |
| C(12) | 0.4854(8) | 0.3962(4) | 0.9166(6) | 0.0697 |
| C(13) | 0.2286(9) | 0.6191(4) | 0.6962(6) | 0.0750 |
| C(3a) | 0.3413(6) | 0.4038(3) | 0.5440(5) | 0.0440 |
| C(6a) | 0.2255(7) | 0.4290(3) | 0.3115(5) | 0.0512 |
| C(7a) | 0.1184(7) | 0.5470(3) | 0.2476(5) | 0.0509 |
| C(11a) | 0.1538(6) | 0.5759(3) | 0.3757(5) | 0.0466 |
| C(11b) | 0.2257(6) | 0.5293(3) | 0.4894(5) | 0.0445 |
| C(11c) | 0.2642(7) | 0.4549(3) | 0.4498(5) | 0.0452 |

Table 4

Interatomic Distances (Å) of **12**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 0(1) | - | C(3) | 1.373(6) | 0(1) | - | C(12) | 1.437(6) |
| 0(2) | - | C(13) | 1.200(6) | 0(7) | - | C(6a) | 1.368(6) |
| 0(7) | - | C(7a) | 1.385(6) | C(l) | - | C(2) | 1.422(7) |
| C(l) | - | C(13) | 1.449(8) | C(l) | - | C(11b) | 1.402(7) |
| C(2) | - | C(3) | 1.356(7) | C(3) | - | C(3a) | 1.423(7) |
| C(4) | - | C(5) | 1.383(7) | C(4) | - | C(3a) | 1.392(7) |
| C(5) | - | C(6) | 1.395(8) | C(6) | - | C(6a) | 1.366(7) |
| C(8) | - | C(9) | 1.462(9) | C(8) | - | C(7a) | 1.487(7) |
| C(9) | - | C(10) | 1.300(1) | C(10) | - | C(11) | 1.466(9) |
| C(11) | - | C(11a) | 1.504(7) | C(3a) | - | C(11c) | 1.413(7) |
| C(6a) | - | C(11c) | 1.409(7) | C(7a) | - | C(11a) | 1.337(7) |
| C(11a) | - | C(11b) | 1.470(7) | C(11b) | - | C(11c) | 1.440(7) |

Table 5

Bond angles (degrees) of **12**

| | | | | | |
|---|---|---|---|---|---|
| C(12) | - | 0(1) | - | C(3) | 116.4(4) |
| C(13) | - | C(l) | - | C(2) | 113.3(5) |
| C(11b) | - | C(l) | - | C(13) | 125.9(5) |
| C(2) | - | C(3) | - | 0(1) | 125.1(5) |
| C(3a) | - | C(3) | - | C(2) | 120.8(5) |
| C(6) | - | C(5) | - | C(4) | 120.8(5) |
| C(7a) | - | C(8) | - | C(9) | 112.3(6) |
| C(11) | - | C(10) | - | C(9) | 125.3(7) |
| C(l) | - | C(13) | - | 0(2) | 124.8(6) |
| C(11c) | - | C(3a) | - | C(3) | 117.3(5) |
| C(6) | - | C(6a) | - | 0(7) | 116.0(5) |
| C(11c) | - | C(6a) | - | C(6) | 123.6(5) |
| C(11a) | - | C(7a) | - | 0(7) | 123.5(5) |
| C(7a) | - | C(11a) | - | C(11) | 117.4(5) |
| C(11b) | - | C(11a) | - | C(7a) | 119.8(5) |
| C(11c) | - | C(11b) | - | C(l) | 116.2(5) |
| C(6a) | - | C(11c) | - | C(3a) | 116.1(5) |
| C(11b ) | - | C(11c ) | - | C(6a ) | 120.7(5) |
| C(7a) | - | 0(7) | - | C(6a) | 119.7(4) |
| C(11b) | - | C(l) | - | C(2) | 120.7(5) |
| C(3) | - | C(2) | - | C(l) | 121.8(5) |
| C(3a) | - | C(3) | - | 0(1) | 114.0(5) |
| C(3a) | - | C(4) | - | C(5) | 119.9(5) |
| C(6a) | - | C(6) | - | C(5) | 118.4(5) |
| C(10) | - | C(9) | - | C(8) | 119.8(7) |
| C(11a) | - | C(11) | - | C(10) | 113.0(5) |
| C(4) | - | C(3a) | - | C(3) | 121.7(5) |
| C(11c) | - | C(3a) | - | C(4) | 121.1(5) |
| C(11c) | - | C(6a) | - | 0(7) | 120.3(5) |
| C(8) | - | C(7a) | - | 0(7) | 109.1(5) |
| C(11a) | - | C(7a) | - | C(8) | 127.4(5) |
| C(11b) | - | C(11a) | - | C(11) | 122.7(5) |
| C(11a) | - | C(11b) | - | C(l) | 127.9(5) |
| C(11c) | - | C(11b) | - | C(11a) | 115.8(5) |
| C(11b) | - | C(11c) | - | C(3a) | 123.2(5) |

## EXPERIMENTAL

Melting points were measured on an Kofler melting-point apparatus and are uncorrected. The nmr spectra were recorded either at 90 MHz (Varian EM 390), at 300 MHz (Bruker AM 300) or at 500 MHz (Bruker AM 500). The various compounds were dissolved in deuteriochloroform (unless otherwise stated) and tetramethylsilane was used as internal reference. For the two dimensional δ $^{13}$C-δ $^1$H correlation experiments, the standard Bruker programs were used, with parameter adjusted to $^1$J or long range coupling. The $^1$H nuclear Overhauser effects were detected by mean of difference experiments. The ir spectra were recorded on a Perkin-Elmer 1720 spectrometer, the uv spectra were measured with a Varian Cary 3E and the mass spectra were obtained with a Ribermag R10-10 C apparatus. Commercially

available reagents and solvents were used without further purification. The yields indicated are the average of at least two experiments.

2-(2-Bromo-5-methoxy-1-naphthyloxy)cyclohexanone (**6**).

To a stirred solution of 2-bromo-5-methoxynaphthol (**5**) [7] (9 g, 35 mmoles) and commercial (Aldrich) 2-chlorocyclohexanone (9.5 g, 71 mmoles) in dry butanone (150 ml), potassium carbonate (7.5 g, 54 mmoles) was added, then the reaction mixture was gently refluxed for 100 hours. After the usual work-up, the crude product was chromatographed (600 g of 230-400 mesh silica gel, elution with chloroform). The Compound **6** (10.4 g, 84%, after recrystallisation from toluene at -30°), white microcrystals had mp 95-96°; $^1$H nmr (90 MHz, deuteriochloroform): δ 1.50-2.86 (m, 8H, 4 x $CH_2$), 3.96 (s, $OCH_3$), 4.80-5.03 (m, 1H), 6.83 (d, $H_3$, $J_o$ = 9 Hz), 7.30-7.60 (m, $H_6$ and $H_7$), 7.76 (dd, $H_8$, $J_o$ = 9 Hz, $J_m$ = 1.5 Hz), 7.90 (d, $H_4$); ir (deuteriochloroform): ν 1727 cm$^{-1}$ (C=O); uv (ethanol): λ max (log ε) 228 (4.69), 300 (3.91), 315 (3.80), 329 (3.64).

*Anal.* Calcd. for $C_{17}H_{17}BrO_3$: C, 58.45; H, 4.87; Br, 22.92. Found: C, 58.40; H, 4.85; Br, 22.72.

6-Bromo-3-methoxy-8,9,10,11-tetrahydrobenzo[*kl*]xanthene (**7**).

A solution of compound **6** (3.5 g, 10 mmoles) in dichloromethane (350 ml) was slowly added at 0°, under an argon atmosphere, to a well stirred solution of tinIV chloride (17 g, 7.63 ml, 65 mmoles) in dichloromethane (75 ml). The purple colored reaction mixture was then stored at 0° in a refrigerator for 100 hours without stirring. After quenching by ice-water and the usual work-up, the crude product (3.4 g) was chromatographed (300 g of 230-400 mesh silica gel, elution with dichloromethane) successively furnishing 2.25 g (68%) of the cyclized compound **7** and 0.5 g (15%) of recovered starting material. The tetrahydrobenzoxanthene **7**, yellow microcrystals had mp 159-160° (petroleum ether 80-110°); $^1$H nmr (90 MHz, deuteriochloroform): δ 1.70-1.95 (m, 4H, 2 x $CH_2$), 2.20-2.55 (m, 4H, 2 x $CH_2$), 3.91 (s, $OCH_3$), 6.66 (s, $H_1$ and $H_2$), 7.43 (s, $H_4$ and $H_5$). The nmr spectrum in deuterioacetone was less deceptively simple, but only the $H_1$-$H_2$ protons AB system was resolved: δ 1.73-1.90 (m, 4H, 2 x $CH_2$), 2.20-2.53 (m, 4H, 2 x $CH_2$), 3.93 (s, $OCH_3$), 6.70 and 6.85 (2d, $H_1$ and $H_2$, $J_o$ = 8.25 Hz), 7.46 (sl, $H_4$ and $H_5$); uv (ethanol): λ max (log ε) 200 (4.43), 238 (4.35), 245 (4.32), 343 (3.92), 360 (3.82), 380 (3.58); ms: (DCI, $NH_3$) m/z (%) 331-333 ([M + H]$^+$, 100).

*Anal.* Calcd. for $C_{17}H_{15}BrO_2$: C, 61.63; H, 4.53; Br; 24.17. Found: C, 61.50; H, 4.55; Br, 23.98.

The cyclizations of the ether **6** by sulfuric acid or by polyphosphoric acid gave only low yields of the oxaphenalene **7**, respectively 6% and 3%.

6-Bromo-4-formyl-3-methoxy-8,9,10,11-tetrahydrobenzo-[*kl*]xanthene (**8**) and 6-Bromo-1-formyl-3-methoxy-8,9,10,11-tetrahydrobenzo[*kl*]xanthene (**9**).

A solution of the bromo-derivative **7** (1.5 g, 4.5 mmoles) in anhydrous dichloromethane (70 ml) was slowly added, at 0°, to a well-stirred solution of titanium tetrachloride (1.9 g, 1.1 ml, 10 mmoles) and dichloromethyl methyl ether (0.58 g, 0.5 ml, 5 mmoles) in dichloromethane (60 ml). The mixture was then stirred at 20° for 4 hours. After quenching by water (100 ml), the organic layer was separated, carefully washed with water and dried (magnesium sulfate). Evaporation of the solvent left a mixture of the two aldehydes (1.5 g) which was submitted to column chromatography (70 g of 230-400 mesh silica gel; elution with dichloromethane) furnishing the following: a/ the recovered starting product **7** (0.2 g); b/ the *peri*-aldehyde **8** (0.15 g, 9%), yellow crystals had mp 220-221° (ethyl acetate); $^1$H nmr: *cf.* Figure 1; ir (deuteriochloroform): ν 1651 cm$^{-1}$ (CHO); uv (ethanol): λ max (log ε) 208 (4.40), 275 (3.86), 327 (3.64), 3.77 (3.58), 420 (3.64); ms: (DCI, $NH_3$) m/z (%) 359-361 ([M+H]$^+$, 100).

*Anal.* Calcd. for $C_{18}H_{15}BrO_3$: C, 60.16; H, 4.18; Br, 22.28. Found: C, 59.97; H, 4.00; Br, 22.11.

c/ A mixture of the previous aldehyde **8** and its isomer **9** (0.94 g) which is submitted to a second chromatography (250 g of 230-400 mesh silica gel, elution with cyclohexane-ethyl acetate 80/20) furnishing successively: 1) a second crop of the aldehyde **8** (0.5 g, 31%) raising the total yield up to 40% (0.65 g); 2) the aldehyde **9** (0.75 g, 46%), yellow crystals had mp 246-247° (ethyl acetate); $^1$H nmr: *cf.* Figure 1; ir (deuteriochloroform): ν 1662 cm$^{-1}$ (CHO); uv (ethanol): λ max (log ε) 208 (4.44), 230 (4.36), 273 (4.31), 348 (3.73), 426 (4.07); ms: (DCI, $NH_3$) m/z (%) 359-361 ([M+H]$^+$, 100).

*Anal.* Calcd. for $C_{18}H_{15}BrO_3$: C, 60.16; H, 4.18; Br, 22.28. Found: C, 60.05; H, 4.11; Br 22.15.

A reverse order of addition of the reagents (addition of the titanium tetrachloride to a mixture of compound **7** and dichloromethyl methyl ether) gave an increased yield of the aldehyde **9** to the detriment of the *peri* aldehyde **8** (50% and 36% respectively).

4-Formyl-3-methoxy-8,9,10,11-tetrahydrobenzo[*kl*]xanthene (**10**) and 4-Formyl-3-methoxybenzo[*kl*]xanthene (**11**).

A mixture of the brominated aldehyde **8** (0.8 g, 2.2 mmoles), copper powder (10 g) and *n*-caproic acid (70 ml) was refluxed for six hours with efficient stirring. After cooling, the copper was separated by filtration and washed three times with dichloromethane (20 ml). The solvent and caproic acid were evaporated at 100° under vacuum (0.1 Torr) and the crude product was dissolved in chloroform (50 ml). The chloroform solution was washed four times with 1*N* potassium bicarbonate solution (4 x 20 ml) in order to eliminate the remaining caproic acid, then with water (2 x 20 ml). After evaporation of the solvent, the crude product was submitted to column chromatography (350 g of 230-400 mesh silicagel). A first elution with cyclohexane-ethyl acetate 80/20 furnished 40 mg (6%) of the formyl tetrahydrobenzoxanthene **10**, as yellow needles, mp 174-175° (ethyl acetate); $^1$H nmr (90 MHz, deuteriochloroform): δ 1.68-1.88 (m, 4H, 2 x $CH_2$), 2.13-2.48 (m, 4H, 2 x $CH_2$), 3.90 (s, $OCH_3$), 6.65 (d, $H_2$, $J_o$ = 8.5 Hz), 6.95 (d, $H_6$, $J_o$ = 9 Hz), 7.10 (d, $H_1$), 8.03 (d, $H_5$), 10.95 (s, CHO); ir (deuteriochloroform): ν 1651 cm$^{-1}$ (CHO); uv (ethanol): λ max (log ε) 205 (4.58), 262 (4.15), 311 (3.78), 324 (3.93), 419 (4.03); ms: (DCI, $NH_3$) m/z (%) 281 ([M+H]$^+$, 100).

*Anal.* Calcd. for $C_{18}H_{16}O_3$: C, 77.14; H, 5.71. Found: C, 77.09; H, 5.60.

Continuation of the elution with ethyl acetate afforded the aromatized formylbenzoxanthene **11** (470 mg, 76%) as yellow needles, mp 201-202° (ethyl acetate); $^1$H nmr (90 MHz, deuteriochloroform): δ 3.96 (s, $OCH_3$), 6.85-7.26 (m, 5H), 7.60 (d, 1H, $J_o$ = 8.2 Hz), 7.75 (dd, 1H, $J_o$ = 8.2 Hz, $J_m$ = 2.5 Hz), 8.05 (d, $H_5$, $J_o$ = 8.2 Hz), 11.00 (s, CHO); ir (deuteriochloroform): ν 1667 cm$^{-1}$ (CHO); uv (ethanol): λ max (log ε) 221 (4.71), 241

(4.59), 361 (4.06), 396 (4.20); ms: (DCI, $NH_3$) m/z (%) 277 ($[M+H]^+$, 100).

*Anal.* Calcd. for $C_{18}H_{12}O_3$: C, 78.26; H, 4.34. Found: C, 78.25; H, 4.25.

1-Formyl-3-methoxy-8,9,10,11-tetrahydrobenzo[*kl*]xanthene (**12**) and 1-Formyl-3-methoxybenzo[*kl*]xanthene (**13**).

The debromination of the aldehyde **9** (1 g, 2.7 mmoles) was carried out with copper powder (12.5 g) in refluxing *n*-caproic acid (85 ml) for six hours as described above for aldehyde **8**. The crude product was chromatographed (375 g of 230-400 mesh silicagel, elution with chloroform) furnishing successively: a) the aromatized debrominated aldehyde **13** (238 mg, 31%), yellow needles, mp 153-154° (ethyl acetate); $^1H$ nmr (90 MHz, deuteriochloroform): δ 4.03 (s, $OCH_3$), 7.03-7.85 (m, 8H), 10.35 (s, CHO); ir (deuteriochloroform): ν 1666 $cm^{-1}$ (CHO); uv (ethanol): λ max (log ε) 204 (4.57), 224 (4.54), 274 (4.41), 339 (3.71), 356 (3.79), 424 (4.03).

*Anal.* Calcd. for $C_{18}H_{12}O_3$: C, 78.26; H, 4.34. Found: C, 78.25; H, 4.20.

b) The tetrahydro aldehyde **12** (230 mg, 29%), yellow needles had mp 165-166° (ethyl acetate); $^1H$ nmr (90 MHz, deuteriochloroform): δ 1.53-1.96 (m, 4H, 2 x $CH_2$), 2.33-2.60 (m, 4H, 2 x $CH_2$), 3.95 (s, $OCH_3$), 6.90 (dd, $H_6$, $J_o$ = 8.25 Hz, $J_m$ = 1.7 Hz), 7.15 (s, $H_2$), 7.43 (t, $H_5$), 7.61 (dd, $H_4$, $J_o$ = 8.25 Hz, $J_m$ = 1.5 Hz), 10.46 (s, CHO); ir (deuteriochloroform): ν 1627 $cm^{-1}$ (CHO); uv (ethanol): λ max (log ε) 202 (4.42), 222 (4.20), 272 (4.38), 347 (3.70), 366 (3.73), 426 (4.12).

*Anal.* Calcd. for $C_{18}H_{16}O_3$: C, 77.14; H, 5.71. Found: C, 77.21; H, 5.65.

4-Formyl-3-hydroxybenzo[*kl*]xanthene (**14**).

A solution of the *peri*-aldehyde **11** (0.4 g, 1.4 mmoles) in dichloromethane (10 ml) was added dropwise, at 20°, to a stirred suspension of aluminum chloride (4 g, 30 mmoles) in dichloromethane (10 ml). The mixture was stirred for 100 additional hours, then quenched with ice-water. After the usual work-up, the crude product (0.33 g) was filtered through a short silica gel column (50 g, chloroform). The aldehyde **14** (0.335 g, 88%) had mp 230-231° (red crystals from ethyl acetate); $^1H$ nmr (90 MHz, deuteriochloroform, assignments were made by spin decoupling experiments): δ 6.90 (d, $H_2$, $J_o$ = 8.25 Hz), 7.15-7.31 (m, 5H, $H_6$ and $H_{8-11}$), 7.81 (d, $H_1$), 7.87 (d, $H_5$, $J_o$ = 8.25 Hz), 9.50 (d, CHO, $J_{CHO-OH}$ = 1.5 Hz), 12.33 (d, OH); ir (deuteriochloroform): ν 1641 $cm^{-1}$ (CHO); uv (ethanol): λ max (log ε) 219 (4.47), 241 (4.28), 356 (3.73), 423 (3.87); ms: (DCI, $NH_3$) m/z (%) 263 ($[M + H]^+$, 100).

*Anal.* Calcd. for $C_{17}H_{10}O_3$: C, 77.86; H, 3.81. Found: C, 77.76; H, 3.78.

1-Benzopyrano[6,5,4-*mna*]xanthene-2-carboxylic Acid (**15**) and 1-Benzopyrano[6,5,4-*mna*]xanthene (**3**).

A mixture of the above aldehyde **14** (0.315 g, 1.2 mmoles), ethyl bromoacetate (0.334 g, 0.22 ml, 2 mmoles), potassium carbonate (0.47 g, 3.4 mmoles) and dimethylformamide (15 ml) was gently refluxed for 3 hours with stirring. After cooling to 80°, 2 ml of a 1M aqueous potassium carbonate solution was added and the mixture was then refluxed for one hour with stirring. After elimination of the solvents (100°, 0.1 Torr) the crude residue was suspended in 100 ml of water and 50 ml of toluene was added. After stirring for 15 minutes, the insoluble sodium salt of the acid **15** was removed by filtration and the toluene solution was reserved. The sodium salt was re-suspended in water (50 ml) and hydrochloric acid (10 *N*, 1 ml) was added. The free acid **15** (0.285 g, 78%), separated by centrifugation, had mp > 260° (deep red microcrystals); $^1H$ nmr (300 MHz, DMSO-$d_6$): δ 6.56 (s, $H_3$), 6.58-7.72 (m, 8H), $CO_2H$ indiscernible; ir (potassium bromide): ν 1688 $cm^{-1}$ ($CO_2H$); uv (ethanol): λ max (log ε) 211 (4.30), 232 (4.29), 388 (3.88).

*Anal.* Calcd. for $C_{19}H_{10}O_4$: C, 75.49; H, 3.31. Found: C, 75.28; H, 3.15.

The toluene solution (see above), after washing with water and drying (magnesium sulfate) was evaporated and the crude 1,6-dioxabenzo[*a*]pyrene **3** was chromatographed (20 g of 230-400 mesh silica gel, elution with chloroform) furnishing 23 mg (7.5%) of pure **3**, as pale yellow crystals, mp 139-140° (pentane); $^1H$ nmr (500 MHz, deuteriochloroform): data given in Table 1; uv (ethanol): λ max (log ε) 207 (4.74), 224 (4.72), 382 (4.14), 406 (4.03), 435 (3.47).

*Anal.* Calcd. for $C_{18}H_{10}O_2$: C, 83.72; H, 3.87. Found: C, 83.65; H, 3.77.

Decarboxylation of the 1-Benzopyrano[6,5,4-*mna*]xanthene-2-carboxylic Acid (**15**).

A mixture of the acid **15** (0.163 g, 0.54 mmoles), copper powder (0.33 g) and quinoline (6 ml) was refluxed for 30 minutes. After the usual work-up, the crude product was dissolved in chloroform and the solution was filtered through a short silica gel column. After evaporation of the solvent, the residue was purified by a second chromatography (20 g of 230-400 mesh silica gel, elution with pentane-dichloromethane 80/20). The 1,6-dioxabenzo[*a*]pyrene (**3**) (60 mg, 43%) had mp 139-140°.

2-(5-Methoxy-1-naphthyloxy)cyclohexanone (**16**).

To a stirred solution of 5-methoxy-1-naphthol (**4**) [6] (1.7 g, 10 mmoles) and commercial (Aldrich) 2-chlorocyclohexanone (1.5 g, 11 mmoles) in dry butanone (20 ml), potassium carbonate (1.6 g, 11 mmoles) was added, then the reaction mixture was gently refluxed for 80 hours. After the usual work-up, the crude product was chromatographed (20 g of 230-400 mesh silica gel, elution with chloroform). The compound **16** (1.1 g, 41%, after recrystallization from toluene at -30°) had mp 123-124°; $^1H$ nmr (90 MHz, deuteriochloroform): δ 1.48-2.85 (m, 8H, 4 x $CH_2$), 4.00 (s, $OCH_3$), 4.75 (t, 1H, J = 6 Hz), 6.76 (m, $H_2$ and $H_6$), 7.36 (m, $H_3$ and $H_7$), 7.86 (dd, $H_8$, $J_o$ = 8.2 Hz, $J_m$ = 1.5 Hz), 7.95 (dd, $H_4$, $J_o$ = 8.2 Hz, $J_m$ = 1.5 Hz); ir (deuteriochloroform): ν 1728 $cm^{-1}$ (CHO); uv (ethanol): λ max (log ε) 226 (4.83), 294 (4.01), 311 (3.87), 326 (3.77).

*Anal.* Calcd. for $C_{17}H_{18}O_3$: C, 75.55; H, 6.66. Found: C, 75.57; H, 6.50.

4-Methoxy-7,8,9,10-tetrahydrobenzo[*b*]naphtho[2,1-*d*]furan (**17**).

A solution of compound **16** (0.35 g, 1.3 mmoles) in dichloromethane (20 ml) was slowly added at 0°, under argon atmosphere, to a well-stirred solution of tinIV chloride (0.65 g, 0.3 ml, 2.5 mmoles) in dichloromethane (20 ml). The purple-colored solution was stirred at 0° for 8 hours, then quenched with ice-water and stirred for 2 hours. After the usual work-up, the crude product (0.33 g) was recrystallized from pentane at -30° furnishing the compound **17** (0.24 g, 73%) as pale yellow crystals, mp 129-130°; $^1H$ nmr (90 MHz, deuteriochloroform): δ

1.90 (m, 4H, 2 x $CH_2$), 2.60-2.90 (m, 4H, 2 x $CH_2$), 3.96 (s, $OCH_3$), 6.75 (d, $H_6$, $J_o$ = 8.25 Hz), 7.33-7.56 (m, $H_2$ and $H_3$), 7.85 (dd, $H_1$, $J_o$ = 8.25 Hz, $J_m$ = 1.5 Hz), 8.06 (d, $H_5$); uv (ethanol): λ max (log ε) 201 (4.33), 261 (4.70), 291 (3.83), 326 (3.41), 341 (3.45).

*Anal.* Calcd. for $C_{17}H_{16}O_2$: C, 80.95; H, 6.35. Found: C, 80.91; H, 6.17.

1-Formyl-3-hydroxybenzo[*kl*] xanthene (**18**).

A mixture of the aldehyde **13** (80 mg, 0.3 mmole) and anhydrous pyridinium chloride (5.5 g, 47 mmoles) was refluxed for 5 minutes, then poured into cold water (50 ml). After the usual work up, the crude product (60 mg) was purified through column chromatography (22 g of 230-400 mesh silica gel, elution with cyclohexane-ethyl acetate 60/40), furnishing 30 mg (40%) of the hydroxyaldehyde **18**, brown crystals (from cyclohexane-ethyl acetate 60/40 at -30°), mp 215-216°; $^1H$ nmr (90 MHz, deuteriochloroform-DMSO-$d_6$ 90/10): δ 7.13-7.86 (m, 8H arom), 10.02 (bs, OH), 10.48 (s, CHO); ir (potassium bromide): ν 1653 $cm^{-1}$ (CHO); uv (ethanol): λ max (log ε) 204 (4.63), 225 (4.58), 276 (4.45), 344 (3.82), 361 (3.90), 429 (4.03).

*Anal.* Calcd. for $C_{17}H_{10}O_3$: C, 77.86; H, 3.81. Found: C, 77.75; H, 3.76.

X-Ray Crystallography of Aldehyde **12**.

Crystallographic and refinement parameters are summarized in Table 2. The data were collected on a Nonius CAD 4 diffractometer using graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å). Two standard reflections were measured every two hours, no change was observed. The structure was solved by direct methods and subsequent Fourier maps. Refinements were carried out by full-matrix least squares techniques. Non-hydrogen atoms were anisotropically refined. All hydrogen atoms positions were found on difference maps, their coordinates were not refined and they were given an overall isotropic thermal parameter. An absorption correction was applied with the DIFABS program [13] from CRYSTALS [14] which has been used to carry out all the calculations. The final atomic parameters for non-hydrogen atoms are reported in Table 3. Bond lengths and bond angles are listed in Tables 4 and 5, respectively. The view of the molecule was performed using Cameron [15].

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