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Synthesis, NMR, molecular modeling and X-ray analysis of a new 1,2,3-tri(4-quinolyl)cyclopropane

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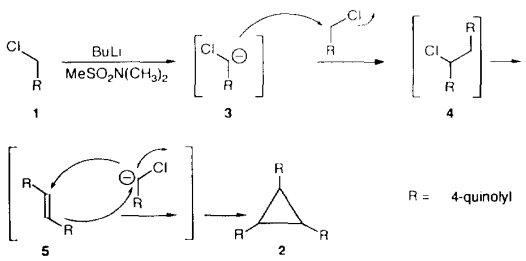
Summary – The structure of *trans*-1,2,3-tri(4-quinolyl)cyclopropane has been determined by homonuclear ^{1}H-^{1}H COSY and heteronuclear ^{13}C-^{1}H chemical shift correlation spectroscopy. This was confirmed by NOE (differential NOE and NOESY). The crystal structure (space group ($C2/C$), a = 26.194(2), b = 7.912(2), c = 23.830(1) Å, β = 96.11(3)°) was solved by X-ray diffraction using the direct method and refined by a least squares procedure. This led to an R factor of 0.065 for 2 810 independent reflections. The spatial arrangement of the quinoline rings observed by X-ray and that obtained by computer modeling are conformationally consistent.

NMR / molecular modeling / X-ray

Introduction

During the course of our work on quinoline derivatives [1], we have observed that the treatment of 4-chloromethylquinoline **1** by *N*,*N*-dimethylmethanesulfonamide in the presence of butyllithium does not lead to the expected nucleophilic substitution product but to the cyclopropane derivative **2**. A possible mechanistic explanation for the formation of **2** is given in scheme 1. It involves a Michael addition of the anion of 4-(chloromethyl)quinoline **3** to the olefin **5**, which is presumably formed by the reaction of the above anion with an unionized molecule **1**. The Michael addition yields a chloroethane derivative **4**, which loses HCl thus accounting for the formation of **2**. A similar reaction leading to the unexpected formation of a cyclopropyl derivative was described by Breslow and Crispino [2, 3]. The *trans* structure of **2** was assigned on the basis of its ^{1}H NMR spectrum, in which two signals appear for the cyclopropyl hydrogen atoms because they are not chemically and magnetically equivalent.



Scheme 1. Formation of **2**.

In order to determine the relative spatial positions of the three quinoline rings of **2**, which was not achievable by NMR studies, we have conducted the first X-ray crystallographic study of **2**. The structure was comparable to that obtained by molecular modeling calculations.

Results and discussion

The ^{1}H NMR spectrum (table I) of compound **2** shows 14 groups for 21 protons : five well-defined signals corresponding to five hydrogens and five overlapping signals at 8.64, 8.21, 7.98, 7.04 and 3.77, corresponding to the other 10 hydrogen atoms.

Four overlapping signals between 7.58 and 7.41 reveal the presence of the six remaining hydrogen atoms. The observed vicinal coupling constant of 6.2 Hz at 3.91 ppm for the cyclopropyl hydrogen H30 is in agreement with a *trans* configuration [4] and was confirmed by NOE (differential NOE and NOESY). However, the coupling constant between H16, H28 and H30 does not confirm a *trans* configuration. Indeed, the value observed by

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Table I. ^{1}H and ^{13}C NMR chemical shifts (δ ppm, $CDCl_3$ with internal reference) of **2**[a].

	^{1}H NMR		
H9, H18	8.64	H27	8.96
H8, H17	7.04	H26	7.52
H5, H14	8.21	H23	8.09
H4, H13	7.41	H22	7.55
H3, H12	7.58	H21	7.72
H2, H11	7.98	H20	8.21
H28, H29	3.77	H30	3.91
	^{13}C NMR		
C9, C18	149.45	C27	130.31
C8, C17	118.99	C26	118.65
C7, C16	141.54	C25	145.66
C6, C15	128.06	C24	128.10
C5, C14	123.30	C23	123.58
C4, C13	126.55	C22	127.17
C3, C12	128.28	C21	129.63
C2, C11	130.11	C20	130.29
C1, C10	148.00	C19	148.25
C28, C29	30.0	C30	23.0

[a] For the sake of comparison we used the numbering of the X-ray structure reported in figure 1a.

Breslow and Crispino (8.6 Hz) is intermediate between that of a *trans* structure (4-9.6 Hz) and that of a *cis* structure (7.0-12.6 Hz) [4]. It is noteworthy that the positions of H5 and H14 (8.21 ppm) and H8 and H17 (7.04 ppm) and reversed from those observed in 4-methylquinoline, where H5 and H8 appeared at 7.95 and 8.04 ppm, respectively. However, the signals for H23 (8.09 ppm) and H20 (8.21 ppm) pertaining to quinoline Q3 (see below) are identical to the corresponding H5 and H8 protons of 4-methylquinoline. The very strong upfield shift of protons H8 and H17 can be explained by the influence of the shielding cone lying above the nearly *cis* quinoline ring.

The ^{13}C NMR spectrum of compound **2** shows 20 resolved lines, including overlapping signals at δ (ppm) 30.0, 130.11, 128.28, 126.55, 123.3, 128.06, 141.54, 118.99, 148.0 and 149.45, which reveal the presence of 30 carbon atoms in the molecular framework. The proton-coupled ^{13}C and DEPT 135 ^{13}C spectra permit the unambiguous assignment of all the methyl, methylene, methine and quaternary carbons. The final support for structure **2** was found using 2D spectra using ^{1}H-^{1}H homonuclear (COSY) and direct ^{13}C-^{1}H heteronuclear (XHCORR) correlations.

Although predicted NOE (table II) are not simple in three-membered rings [5, 6], they were in full agreement with observed signals and confirmed the *trans* configuration of **2**.

However, NMR studies did not allow the determination of the angular positions of the three quinoline rings with respect to the cyclopropane. We therefore decided to determine the X-ray structure of **2** and compare it with that obtained by molecular modeling.

The X-ray structure of **2** consisted of a cyclopropane ring (fig 1a) with its three ternary hydrogens replaced by three 4-quinoline groups Q_1, Q_2 and Q_3 (where Q_1, Q_2 and Q_3 stand for the atom groups defined by (N(1)-C(2)...C(9)), (N(2)-C(11)...C(18)) and (N(3)-C(20)...C(27), respectively). The bond distances and angles (tables III, IV and V) indicate that the rings in the Q_i groups are fairly regular with maximum deviations from average values of less than 0.02 Å. As expected, the atoms in each Q_i group are practically planar (maximum deviation from the mean plane of 0.05 Å for C(8)). The quinoline planes adopt a *trans* position with respect to the cyclopropane plane (fig 1a). The angles formed by the Q_1, Q_2 and Q_3 mean planes with that of cyclopropane are 54.5°, 66° and 57.9°, respectively. These values are significantly different from those given by energy-minimized modeling of the isolated molecule (fig 1b), 85.8, 36.8 and 30.2°, respectively.

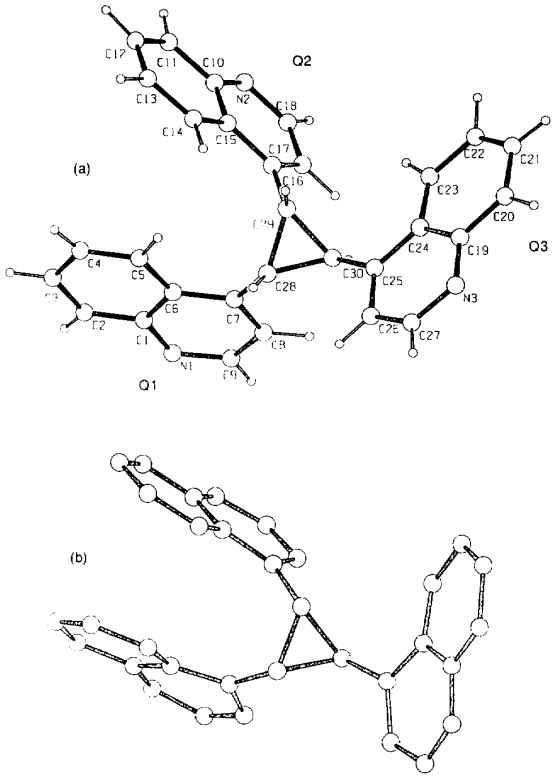

Fig 1. Molecular structure representations (PLUTON [7]) of *trans*-1,2,3-tri(4-quinolyl)cyclopropane by (a) X-ray diffraction data and (b) computer modeling. Note the different orientations of Q planes in (a) and (b).

It is still unclear whether these differing values are due to the inappropriate force constants used in the energy calculation or due to the effect of intermolecular packing energy, which were not taken into account in the modeling of the isolated molecule.

It should be noted that no hydrogen bonds are found in the molecular structure of **2**. The packing force are mostly ensured by strong interactions mediated by parallel phenyl rings. Two quinoline planes (Q_1 and Q_3) of the molecule are parallel to their centrosymmetrically related equivalents (Q_1' and Q_3'). The third quinoline plane, Q_2, makes an angle of 34° with its 2_1-counterpart

Table II. Predicted NOE based on Dreiding models.

trans Configuration	*cis* Configuration
H28, H29 with H30	H29 with H5
H30, H17 with H8	H8 with H17 and H26
H28, H29 with H14 and H5, respectively	H14, H23 with H29 and H30, respectively
H28, H29 with H8 and H17, respectively	H28, H29 with H8 and H17, respectively
H8, H17 with H20	H14 with H23
H26 with H5 and H14	H8, H17 and H26 with H-5 and H14 and H23, respectively

Q'_2 (fig 2). The distances between Q_1 and Q'_1 between Q_3 and Q'_3 are 4.22 and 3.88 Å, respectively. In addition, the solvent species are in a channel left by space-filling model of Corey-Pauling-Koltum (referred to as "C40"..."C45") and between the quinoline parallel planes (referred to as "C60"..."C62"). These findings suggest that the solvent molecules may play a crucial role in enhancing the cohesion force of the crystal.

Table III. Atomic coordinates ($\times 10^4$), equivalent isotropic displacement parameters (Å$\times 10^3$) and site occupation factor (SOF) when it is different from one, for *trans*-1,2,3-tri-(4-quinolyl)cyclopropane. U (eq) is defined as one third of the trace of the orthogonalized u_{ij} tensor. Solvent atoms are labeled with an asterisk.

Atom	x	y	z	U(eq)	SOF
N(1)	2 703(1)	−513(3)	644(1)	56(1)	
C(1)	2 731(1)	1 193(3)	735(1)	46(1)	
C(2)	3 219(1)	1 915(3)	869(1)	57(1)	
C(3)	3 274(1)	3 605(4)	974(1)	66(1)	
C(4)	2 839(1)	4 651(4)	940(1)	70(1)	
C(5)	2 361(1)	3 984(3)	806(1)	57(1)	
C(6)	2 290(1)	2 243(3)	705(1)	43(1)	
C(7)	1 801(1)	1 474(3)	586(1)	45(1)	
C(8)	1 783(1)	−239(3)	513(1)	58(1)	
C(9)	2 242(1)	−1 163(4)	542(1)	62(1)	
N(2)	1 679(1)	2 259(4)	2 758(1)	83(1)	
C(10)	1 729(1)	3 805(4)	2 507(1)	69(1)	
C(11)	2 001(1)	5 074(6)	2 830(1)	92(1)	
C(12)	2 070(1)	6 638(6)	2 608(2)	95(1)	
C(13)	1 871(1)	6 989(5)	2 059(2)	85(1)	
C(14)	1 600(1)	5 803(4)	1 733(1)	67(1)	
C(15)	1 530(1)	4 150(3)	1 946(1)	57(1)	
C(16)	1 278(1)	2 827(3)	1 619(1)	52(1)	
C(17)	1 241(1)	1 283(4)	1 881(1)	65(1)	
C(18)	1 442(1)	1 080(5)	2 445(1)	79(1)	
N(3)	−606(1)	3 034(3)	−364(1)	73(1)	
C(19)	−590(1)	2 812(3)	199(1)	57(1)	
C(20)	−1 052(1)	3 011(3)	463(1)	67(1)	
C(21)	−1 058(1)	2 789(4)	1 018(2)	74(1)	
C(22)	−616(1)	2 326(4)	1 359(2)	80(1)	
C(23)	−161(1)	2 138(4)	1 127(1)	68(1)	
C(24)	−131(1)	2 368(3)	548(1)	53(1)	
C(25)	330(1)	2 217(3)	286(1)	52(1)	
C(26)	301(1)	2 457(4)	−280(1)	67(1)	
C(27)	−172(1)	2 858(5)	−583(1)	82(1)	
C(28)	1 323(1)	2 522(3)	520(1)	48(1)	
C(29)	1 066(1)	3 144(3)	1 030(1)	50(1)	
C(30)	818(1)	1 807(3)	640(1)	51(1)	
*C(40)	5 000()	4 078(18)	2 500()	252(12)	
*C(41)	5 449(4)	1 062(24)	2 276(4)	226(9)	
*C(42)	4 374(3)	1 863(13)	1 992(5)	192(5)	
*C(43)	4 999(8)	3 465(14)	2 103(6)	305(12)	
*C(44)	5 000()	1 867(29)	2 500()	376(42)	0.94
*C(45)	5 010(16)	315(24)	2 823(6)	321(22)	0.75
*C(60)	2 584(42)	957(156)	17(40)	395(84)	0.19
*C(61)	386(22)	2 562(57)	4 578(21)	100(19)	0.12
*C(62)	2 223(11)	−2 395(43)	456(13)	113(15)	0.16

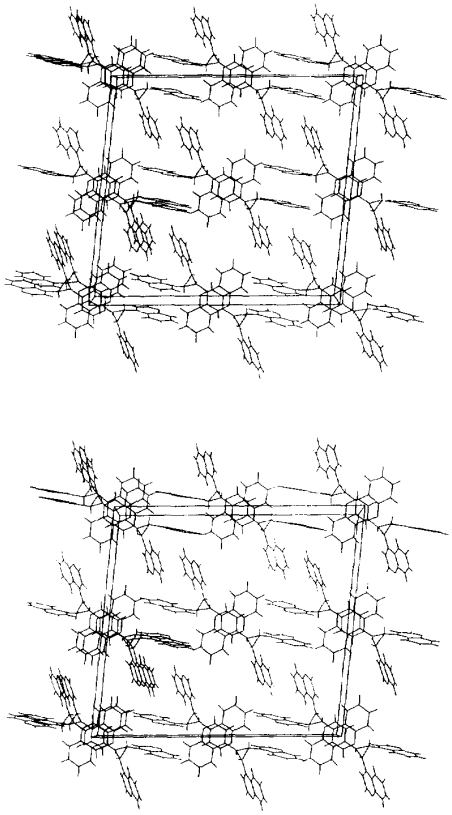

Fig 2. Molecular packing (Pluton [7]) of **2** showing intermolecular interactions between parallel quinoline planes.

Both modeling methods gave an energy of 102.7 kcal/mol for **2**. The corresponding energy for the X-ray structure was substantially higher, 223.9 kcal/mol. This increased energy of 121.2 kcal/mol may be explained by packing forces or by the discrepancy between C-C and C-H bond lengths of the X-ray structure and those from the Tripos force field. Indeed using the X-ray skeleton with C-H bonds from Tripos force field led to an energy of 133.5 kcal. It is worthwhile noting that energy minimization by Sybyl using X-ray coordinates as a starting model allowed us to retrieve the same conformer of 102.7 kcal/mol. The RMS of the superposed structures was 0.018 Å.

Table IV. Selected bond lengths (Å) and angles (°) for *trans*-1,2,3-tri(4-quinolyl)cyclopropane.

N(1)-C(9)	1.312(3)	N(2)-C(18)	1.309(4)	N(3)-C(27)	1.309(4)
N(1)-C(1)	1.368(3)	N(2)-C(10)	1.373(4)	N(3)-C(19)	1.349(4)
C(1)-C(2)	1.406(3)	C(10)-C(15)	1.408(4)	C(19)-C(20)	1.431(4)
C(1)-C(6)	1.419(3)	C(10)-C(11)	1.412(5)	C(19)-C(24)	1.432(4)
C(2)-C(3)	1.365(4)	C(11)-C(12)	1.366(6)	C(20)-C(21)	1.337(4)
C(3)-C(4)	1.405(4)	C(12)-C(13)	1.384(6)	C(21)-C(22)	1.392(4)
C(4)-C(5)	1.364(4)	C(13)-C(14)	1.367(4)	C(22)-C(23)	1.374(4)
C(5)-C(6)	1.408(3)	C(14)-C(15)	1.422(4)	C(23)-C(24)	1.402(4)
C(6)-C(7)	1.418(3)	C(15)-C(16)	1.424(4)	C(24)-C(25)	1.421(4)
C(7)-C(8)	1.367(3)	C(16)-C(17)	1.380(4)	C(25)-C(26)	1.357(4)
C(7)-C(28)	1.495(3)	C(16)-C(29)	1.475(3)	C(25)-C(30)	1.489(3)
C(8)-C(9)	1.400(3)	C(17)-C(18)	1.401(4)	C(26)-C(27)	1.402(4)
		C(28)-C(30)	1.497(3)		
		C(28)-C(29)	1.533(3)		
		C(29)-C(30)	1.509(3)		
C(9)-N(1)-C(1)	116.6(2)	C(18)-N(2)-C(10)	116.6(2)	C(27)-N(3)-C(19)	116.5(2)
N(1)-C(1)-C(6)	122.7(2)	N(2)-C(10)-C(15)	122.9(3)	N(3)-C(19)-C(24)	123.0(2)
C(2)-C(1)-C(6)	119.3(2)	C(15)-C(10)-C(11)	119.6(3)	C(20)-C(19)-C(24)	118.0(3)
C(3)-C(2)-C(1)	121.1(2)	C(12)-C(11)-C(10)	120.8(3)	C(21)-C(20)-C(19)	121.3(3)
C(2)-C(3)-C(4)	119.8(2)	C(11)-C(12)-C(13)	119.8(3)	C(20)-C(21)-C(22)	121.0(3)
C(5)-C(4)-C(3)	120.3(3)	C(14)-C(13)-C(12)	121.3(4)	C(23)-C(22)-C(21)	119.9(3)
C(4)-C(5)-C(6)	121.4(2)	C(13)-C(14)-C(15)	120.5(3)	C(22)-C(23)-C(24)	121.6(3)
C(5)-C(6)-C(1)	118.1(2)	C(10)-C(15)-C(14)	117.9(2)	C(23)-C(24)-C(19)	118.2(3)
C(7)-C(6)-C(1)	118.1(2)	C(10)-C(15)-C(16)	118.7(2)	C(25)-C(24)-C(19)	117.8(3)
C(8)-C(7)-C(6)	118.0(2)	C(17)-C(16)-C(15)	117.1(2)	C(26)-C(25)-C(24)	117.6(2)
C(7)-C(8)-C(9)	119.6(2)	C(16)-C(17)-C(18)	119.8(3)	C(25)-C(26)-C(27)	119.9(3)
N(1)-C(9)-C(8)	124.9(3)	N(2)-C(18)-C(17)	124.9(3)	N(3)-C(27)-C(26)	125.2(3)
		C(30)-C(28)-C(29)	59.7(2)		
		C(30)-C(29)-C(28)	58.93(14)		
		C(28)-C(30)-C(29)	61.33(14)		

Table V. Average bond distances and angles in the quinoline rings. C-C bond distances are slightly increased in the pyridine rings.

	Q1		Q2		Q3	
	A	B	A	B	A	B
d(C-C) (Å)	1.395(4)	1.401(3)	1.393(5)	1.414(4)	1.395(4)	1.425(4)
d(C-N) (Å)		1.340(3)		1.341(4)		1.329(4)
Angle (°)	120.0(2)	120.0(2)	120.0(3)	120.0(3)	120.0(3)	120.0(3)

Furthermore, Q_1 and Q_2 in conformer **2** are nearly parallel (plane angle of *ca* 23°) according to molecular modeling whereas they showed an angle of 65.6° in X-ray analysis. The plane angles between the pyridinyl and the phenyl rings of Q_1 and Q_2 were 7.82° and 6.86° respectively. These results emphasize the asymmetry of the molecule due to the influence of Q_3 on Q_2.

Another explanation of this disparity is the difference in electronic shape between the modeled structure, in which the positive molecular orbital lobes of Q_1 face negative molecular orbital lobes of Q_2, and the X-ray structure, where lobes of the same charge face each other (fig 3).

A deformation can thus occur because of the modification of the electronic repartition of Q_1 and Q_2 compared to Q_3. This happens because of the partial double bond character of the cyclopropane ring, which allows a delocalization between Q_1, Q_2 and the ring, resulting in a more flexible quinoline ring.

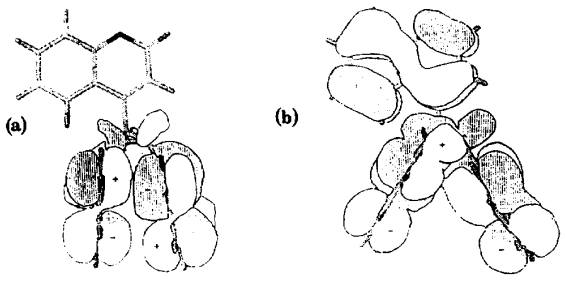

Fig 3. Electronic orbital representations of (a) the minimized molecule **2** and (b) the X-ray structure.

The interaction between quinolines Q_1 and Q_2 in the molecular modeling can be explained by van der Waals forces. The result is a hydrophobic interaction between the phenyl rings of Q_1 and Q_2. This hypothesis can be reinforced by the fact that they are parallel and by the

distance observed between them (3.8 Å), which is the usual distance encountered in such interactions [8].

Conclusion

NMR, X-ray and computer modeling were applied to quinoline derivative **2** and gave consistent results considering general conformation. However, computer and X-ray models differ substantially in terms of quinoline plane orientations. This difference may be attributed to intermolecular interactions. The molecular packing of *trans*-1,2,3-tri(4-quinolyl)cyclopropane indicates no hydrogen bonds. The packing forces are mainly ensured by strong intermolecular interactions mediated by parallel quinoline planes.

Experimental section

IR spectra

The IR spectrum was recorded in the solid state on a Philips Pye-Unicam SP3-100 in the 4 000-600 cm^{-1} region using KBr pellets.

NMR spectra

The ^1H spectra were recorded at 200.13 MHz and the ^{13}C spectra were recorded at 50.33 MHz on a Bruker AC 200 at 21°C. $CDCl_3$ and TMS as internal references.

Mass spectrum

The mass spectrum was recorded on a Nermag R10-10C by FAB with nitrobenzylalcohol.

Molecular modeling

All the computations were performed on a Silicon Graphics workstation with Sybyl 6.03 [9] molecular modeling package. The diastereomer **2** was built using the structure fragment library of Sybyl. The structure was energy-minimized by the Powell method with a dielectric constant of 1 using the Tripos force field. Charges were calculated by the Gasteiger-Hückel method provided by Sybyl.

The conformational space of diastereomer **2** was explored using HTDMS (high temperature molecular dynamic simulation). The minimized structure was used as a starting point for a 20 ps trajectory at a temperature of 1 500 K and a pressure of 3×10^5 N/m^{-2}. The time step was 1 fs and conformers were stored every 5 fs. In order to verify HTDMS simulation, a grid search was performed with angle increments of 30° for each of the three rotating bonds. The 11 lowest energy structures for each energy graph were minimized using the method described above.

Some semi-empirical calculations by the AM1 method (from the Mopac [10] module in Sybyl) were made on the crystallographic structure and the fully optimized related conformer **2** to visualize HOMO.

Superposition of structures was performed by the Match command in Sybyl.

Crystal data

$C_{30}H_{24}N_3$, M = 3 387.98. Monoclinic, a = 26.194(2), b = 7.912(2), c = 23.830(1) Å, β = 96.11(3)°, V = 4 911(1) $Å^3$ (unit-cell dimensions were determined by least-squares method using angular data obtained with a four-circle diffractometer), space group C2/c, Z = 8, Dc = 1.146 mg/m^3, μ(Cu-Kα) = 0.526 cm^{-1}, $F(000)$ = 1 776.

Data collection and processing

A prism fragment (0.48 × 0.48 × 0.20 mm) was used for the intensity data collection, performed with an Enraf-Nonius CAD4 diffractometer operating with Kα copper radiation (1.5418 Å), monochromatized by a graphite plate; 4 298 non-zero reflections ($I > 3\sigma(I)$) were measured with an ω scan of 1.20°, during a maximum time of 80 s, in an angular range of 2 to 62° (θ). Among this set of reflections, 3 831 were independent (R_{int} = 0.02). Intensity and orientation reference reflections showed no significant variation during the data collection. The Lorentz and polarization corrections were applied.

Structure analysis and refinement

Structure determination was undertaken using a direct method : Multan 77 [11]. This method enable us to localize a part of the structure. Successive Fourier-difference syntheses then clearly revealed the whole arrangement of the expected molecules, including the hydrogen atoms. The atomic coordinates and isotropic thermal parameters of the hydrogen atoms were also included in the refinements. In spite of the introduction of all of the presumed arrangements in the refinements, the R-factor at this stage still keeps a relatively high value of 0.126. This fact has incited us to inspect more carefully the Fourier-difference map based on the current structure model, which clearly revealed the presence of additional peaks attributed to residues of initial components and/or of the solvent used for the crystallization of the compound. Efforts to identify the geometry of the solvent peaks suggest they may correspond to the cyclopropane molecule in disordered state. Refinements (on F) using 2 810 reflections corresponding to $I > 4\sigma(I)$, with a unitary weighting scheme (SDP system [12]) were carried out. The addition of these residual atoms in the refinement procedure leads to a relatively satisfactory R-factor value of 0.065. However, the bond lengths and bond angles remained highly dispersed with respect to the average values. This may be attributed to the poor quality of the crystal and/or the inappropriate procedure refinements used in the early stage. Therefore, two new refinement cycles based on F^2 (Shelx 93 [13]) were added : in the first few cycles the molecular model was gently restrained in order to regularize its geometry, while in the final cycles all the atom parameters were freed. These last refinements lead to a R-factor of 6.5% for 2 810 reflections with $F^2 > 4\sigma(F^2)$. Table III gives the atomic coordinates and isotropic thermal factors and tables IV and V contain the selected bond distances and bond angles of **2**.

Synthesis of 1,2,3-tri(4-quinolyl)cyclopropane **2**

BuLi (2.5 M, 3.3 mL) was added to a solution of dimethylmethanesulfonamide (1 g, 8 mmol) in THF (20 mL) at −76°C under a nitrogen atmosphere. After 45 min, a solution of 4-chloromethylquinoline (1.43 g) in THF (20 mL) was slowly added. After 3 h, 20 mL of 5% $NaHCO_3$ was added and the solvent was removed. The residue was partitioned between CH_2Cl_2 and H_2O and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and the residue was purified by flash chromatography (CH_2Cl_2/EtOAc) to yield **2** (315 mg, 28%).

Mp = 194-195°C ($CHCl_3/C_6H_{14}$, 8:2).

IR (ν_{max}, cm^{-1} : 2 960 (C-H); 1 600 (C=N, C=C); 1 500; 1 450; 1 280; 1 050; 950.

m/z 424 (M + 1, 62%) and 283 (M + 1-141, 100%). ^{1}H and ^{13}C NMR data, see table I.

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