Synthesis and Reactivity of (1*S*,4*S*,5*S*)-5-Bromo-1,3,3-trimethyl-*N*-nitro-2-oxabicyclo[2.2.2]octan-6-imine. X-Ray Molecular Structure and Absolute Configuration of *E* and *Z* Isomers of (1*S*,4*S*)-5,5-Dibromo-1,3,3-trimethyl-*N*-nitro-2-oxabicyclo[2.2.2]octan-6-imine, the First Case of Separated Nitrimine Isomers

Angelo Ranise,[a] Francesco Bondavalli,[a] Pietro Schenone,*[,a] Angelo Mugnoli[b] and Marcella Pani[b]

[a] *Istituto di Scienze Farmaceutiche dell'Università, Viale Benedetto XV, 3 I-16132 Genova, Italy*

[b] *Istituto di Chimica Fisica dell'Università, Palazzo delle Scienze, Corso Europa 26, I-16132 Genova, Italy*

The potassium salt **2** of 1,3,3-trimethyl-*N*-nitro-2-oxabicyclo[2.2.2]octan-6-imine **1** reacted with bromine in acetic acid solution to give (1*S*,4*S*,5*S*)-5-bromo-1,3,3-trimethyl-*N*-nitro-2-oxabicyclo[2.2.2]octan-6-imine **3**. Bromination of the salt **2** in methanolic potassium hydroxide afforded a mixture of (1*S*,4*S*)-5,5-dibromo-1,3,3-trimethyl-*N*-nitro-2-oxabicyclo[2.2.2]octan-6*E*- and -6*Z*-imine **4** and **5**, whose X-ray crystal-structure determinations allowed their absolute configurations to be established. Bromination of monobromide **3** under different conditions gave the dibromide **4**, which was converted into isomer **5** by storage in chloroform solution. Nitrimine **3** reacted with hydroxylamine hydrochloride and sodium hydroxide or piperidine to give (1*S*,4*S*,5*S*)-5-bromo- and -5-hydroxyamino-*N*-hydroxy-1,3,3-trimethyl-2-oxabicyclo[2.2.2]octan-6-imine or (1*S*,4*S*,5*S*)-*N*-hydroxy-1,3,3-trimethyl-5-(piperidin-1-yl)-2-oxabicyclo[2.2.2]octan-6-imine. Reaction of compound **3** with aliphatic and aromatic primary amines afforded *N*-substituted (1*S*,4*S*,5*S*)-5-bromo-1,3,3-trimethyl-2-oxabicyclo[2.2.2]octan-6-imines. Reduction of compound **3** with sodium cyanoborohydride gave (1*S*,4*S*,5*S*)-5-bromo-1,3,3-trimethyl-*N*-nitro-2-oxabicyclo[2.2.2]octan-6-amine, whereas consecutive treatment with potassium hydroxide and aq. hydrochloric acid afforded the less stable isomer (1*S*,4*S*)-5-bromo-1,3,3-trimethyl-*N*-nitro-2-oxabicyclo[2.2.2]oct-5-en-6-amine.

In a previous paper[1] we reported the readily occurring reaction of camphor nitrimine as its potassium salt with bromine in both acid and alkaline solutions to give, in high yield, 3-*exo*-bromocamphor nitrimine and 3,3-dibromocamphor nitrimine, respectively. Subsequently, the role of the acid medium in this reaction and the high-yield conversion of the *exo* epimer to the more stable *endo* isomer were further investigated.[2]

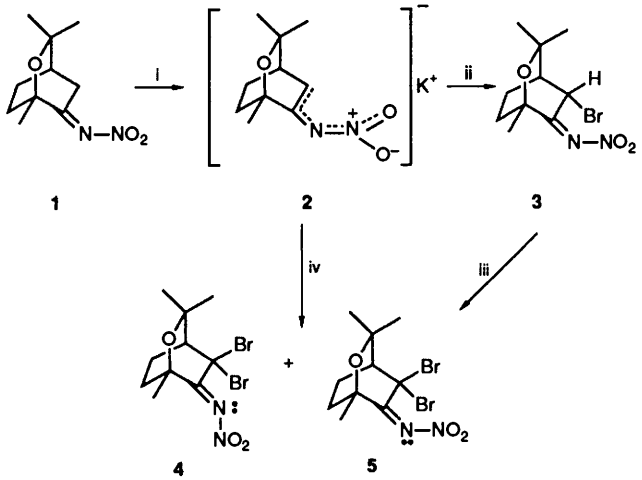
Our current interest in the nitrimino group chemistry[1–4] and in cineole derivatives with pharmacological activity,[5] coupled with the structural correlations between the bicyclic rings of bornane and cineole, prompted us to extend the above reactions of bromine to a cineole nitrimine, namely (1*S*,4*R*)-1,3,3-trimethyl-*N*-nitro-2-oxabicyclo[2.2.2]octan-6-imine **1**.[6]

Results and Discussion

The reaction of nitrimine **1** as its potassium salt **2** with bromine was carried out both in acid (acetic acid) and in strong basic (potassium hydroxide in methanol) solution (Scheme 1).

In the former case, the choice of acetic acid as solvent instead of hydrochloric acid[1] was caused by our further work on bromination of camphor nitrimine potassium salt, whereby this reaction, when carried out in acetic acid solution, gave higher yields of the 3-bromocamphor nitrimines mixture.[2] The bromination of the salt **2** in acetic acid solution gave a higher yield (84%) and a purer product than in conc. hydrochloric acid solution.

The compound obtained was recognized as (1*S*,4*S*,5*S*)-5-bromo-1,3,3-trimethyl-*N*-nitro-2-oxabicyclo[2.2.2]octan-6-imine **3** by the presence of IR absorptions corresponding to C=N and N–NO_2 groups, ^{13}C NMR evidence of a C=N–NO_2 group at δ_C 173.83, and a ^1H NMR doublet at δ_H 5.52 (*J* 4 Hz), quite similar to that of the corresponding 3-*exo*-proton in 3-*endo*-bromocamphor nitrimine.[1]



Scheme 1. *Reagents:* i, KOH; ii, Br_2–AcOH; iii, KOH, then Br_2–AcOH; iv, excess of Br_2–KOH.

Thus, bromination of the salt **2** in acetic acid solution occurred in a stereospecific manner to give the more stable (5*S*)-Br compound, unlike the same reaction with camphor nitrimine in which a 1:1 mixture of 3-*endo*- and 3-*exo*-bromocamphor nitrimines was obtained.[2]

The bromine atom adjacent to the nitrimino group in **3** seems

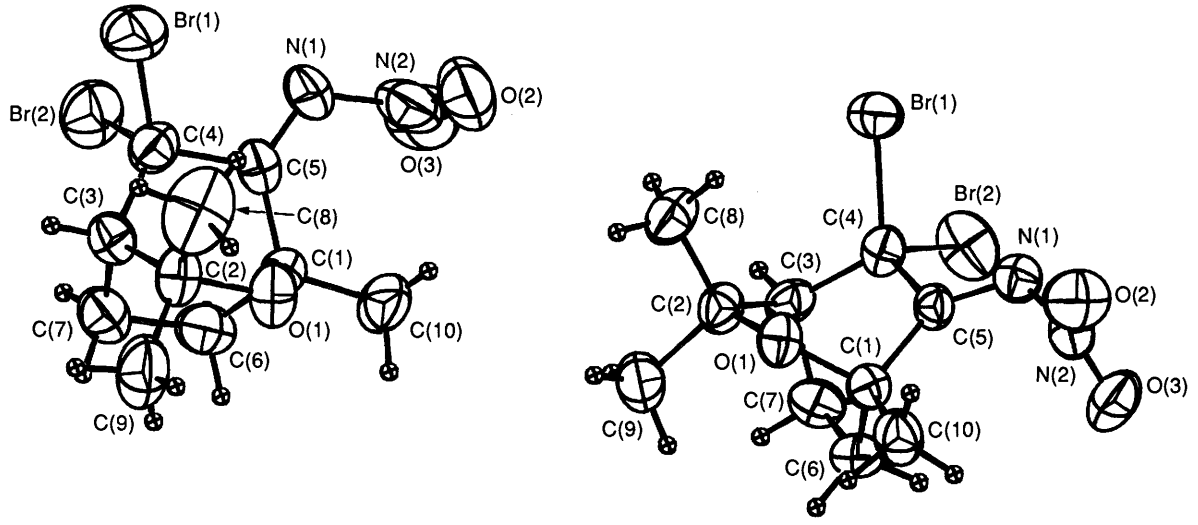


Fig. 1. The two independent molecules A and B of isomer **4**, with thermal ellipsoids at the 0.50 probability level. Hydrogen atoms are drawn as spheres of arbitrary radius.

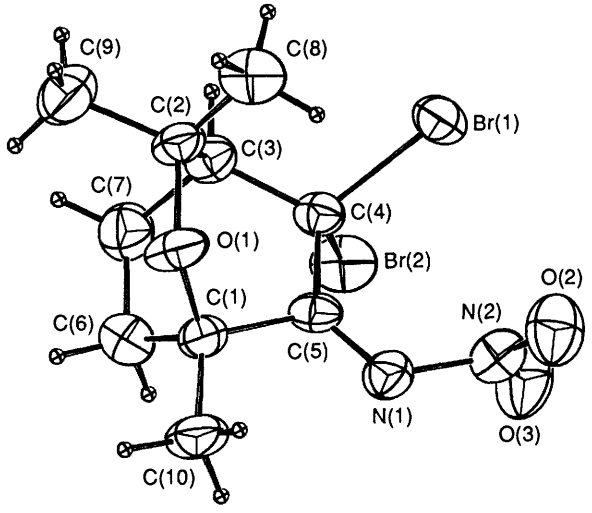


Fig. 2. Atomic numbering for isomer **5**, with thermal ellipsoids at the 0.50 probability level. Hydrogen atoms are drawn as spheres of arbitrary radius.

to stabilize the latter, since the bromonitrimine **3** is stable in the open air at room temperature for several months, unlike nitrimine **1** which decomposed under the same conditions.

When bromination of the salt **2** was carried out in a methanolic solution of potassium hydroxide, a mixture of two dibromo derivatives with m.p. 89–90 °C and 119–120 °C (decomp.), in which the latter predominates, was obtained; the same mixture, but with a prevalence of the former, also resulted by further bromination of bromonitrimine **3** under the same conditions.

On a slight change in the experimental conditions, only the compound with lower m.p. could be obtained, in 83% yield. This compound was found to be a convertible isomer of that with higher m.p., since it was entirely transformed into the latter when left at room temperature for a week in chloroform solution. Attempts to hasten this conversion by reflux of chloroform or toluene solutions of the compound with lower m.p. failed, probably owing to the decomposition trend of the isomer with higher m.p. The conversion could also be observed by slow heating of the compound with lower m.p. after it had melted: the liquid solidified and remelted at 113–115 °C (decomp.). We confirmed that the two compounds with m.p. 89–90 °C and 118–120 °C (decomp.) are geometric isomers, namely (1*S*,4*S*)-5,5-dibromo-1,3,3-trimethyl-*N*-nitro-2-oxabicyclo-[2.2.2]octan-6*E*-imine **4** and -6*Z*-imine **5**, respectively, on the following grounds. Elemental analyses are in agreement with the molecular formula $C_{10}H_{14}Br_2N_2O_3$ for both compounds; also IR spectra are practically the same, showing the absorptions of C=N and N–NO_2 groupings, whereas the ^{13}C NMR spectra are similar, revealing the presence of the C=N–NO_2 group at δ_C 165.96 and 173.71 in the case of the higher and lower m.p. isomer, respectively.

The crystal-structure determinations do establish unambiguously the configurational isomerism of the two moieties: with respect to the C(4)–C(5) bond, the N(1)–N(2) bond is in the *E* configuration in the isomer of m.p. 89–90 °C **4** and in the *Z* configuration in the isomer of m.p. 118–120 °C **5** (Figs. 1 and 2). The X-ray diffraction data allowed us to establish the absolute configuration of both **4** and **5**. On these grounds the absolute configuration has been extended also to compounds **1–3** and **6–15**. We want to emphasize that, to our knowledge, this is the first case in which the separation of *E* and *Z* isomers of the C=N–NO_2 group has been successfully achieved (*cf.* ref.7).

Crystal Structure of Compounds **4** *and* **5**.—Drawings of the lower and higher melting isomers are reported in Figs. 1 and 2, respectively; only the content of the asymmetric unit is shown, namely two molecules of compound **4** and one molecule of compound **5**. The pictures were obtained by means of the ORTEP program.[8] The final atomic co-ordinates of non-hydrogen atoms with their corresponding e.s.d.s are listed for the two isomers in Tables 1 and 2; selected bond lengths, bond angles, and dihedral angles between least-squares planes are reported in Tables 3–5.*

A typical feature of the known structures of nitrimine

* *Supplementary data* (see section 5.6.3 of Instructions for Authors in the January issue). A full list of anisotropic thermal parameters of non-hydrogen atoms, bond lengths, bond angles, and hydrogen atom co-ordinates have been deposited at the Cambridge Crystallographic Data Centre.

Table 1. Fractional atomic co-ordinates ($\times 10^4$) for compound **4**, with e.s.d.s in parentheses.

	x	*y*	*z*
C(1A)	2058(9)	5092(7)	4742(2)
C(2A)	1602(10)	3490(5)	4204(2)
C(3A)	418(10)	4459(7)	4026(3)
C(4A)	−874(11)	4838(7)	4391(3)
C(5A)	143(11)	5037(7)	4828(3)
C(6A)	2400(11)	5902(8)	4339(3)
C(7A)	1529(12)	5498(8)	3902(3)
C(8A)	768(10)	2402(5)	4361(2)
C(9A)	2984(10)	3180(5)	3860(2)
C(10A)	3232(9)	5348(7)	5140(2)
Br(1A)	−2813(2)	3805(1)	4468(0)
Br(2A)	−2007(2)	6313(1)	4245(0)
N(1A)	−783(10)	5120(8)	5185(3)
N(2A)	94(12)	5384(12)	5610(3)
O(1A)	2500(8)	3934(5)	4607(2)
O(2A)	351(12)	4557(10)	5848(3)
O(3A)	266(10)	6397(9)	5696(3)
C(1B)	7930(9)	4941(5)	7103(3)
C(2B)	5548(7)	5632(6)	6628(2)
C(3B)	5802(10)	6592(6)	6983(3)
C(4B)	5623(9)	6156(6)	7465(2)
C(5B)	7004(9)	5211(6)	7547(2)
C(6B)	8893(10)	6035(7)	6979(3)
C(7B)	7628(11)	7052(7)	6940(3)
C(8B)	3728(7)	5185(6)	6556(2)
C(9B)	6200(7)	5996(6)	6156(2)
C(10B)	9109(9)	3903(5)	7096(3)
Br(1B)	3365(1)	5526(1)	7652(0)
Br(2B)	5985(2)	7390(1)	7906(0)
N(1B)	7141(8)	4869(6)	7951(2)
N(2B)	8497(10)	4071(7)	8055(2)
O(1B)	6576(7)	4675(4)	6783(2)
O(2B)	8085(8)	3079(6)	8091(2)
O(3B)	9881(8)	4487(6)	8139(2)

Table 2. Fractional atomic co-ordinates ($\times 10^4$) for compound **5**, with e.s.d.s in parentheses.

	x	*y*	*z*
C(1)	8 312(9)	2 552(3)	8 407(3)
C(2)	8 764(8)	1 926(4)	6 829(3)
C(3)	6 781(8)	1 448(3)	7 167(3)
C(4)	7 129(8)	831(3)	8 045(3)
C(5)	8 276(7)	1 476(3)	8 722(3)
C(6)	6 227(11)	2 905(4)	8 184(4)
C(7)	5 309(10)	2 283(4)	7 404(4)
C(8)	10 453(10)	1 238(4)	6 577(4)
C(9)	8 386(11)	2 589(5)	5 984(4)
C(10)	9 329(11)	3 212(4)	9 088(3)
Br(1)	8 370(1)	−446(0)	7 812(0)
Br(2)	4 536(1)	480(1)	8 635(0)
N(1)	9 184(7)	1 286(3)	9 475(3)
N(2)	9 292(8)	284(3)	9 812(3)
O(1)	9 523(7)	2 542(3)	7 581(2)
O(2)	10 909(7)	−87(3)	9 797(3)
O(3)	7 808(7)	−37(3)	10 176(3)

derivatives is a R–C=N bond angle of 131 ± 7°,* where R is a C or N atom *cis* to the nitro group. Our results lie within this range (see Table 4). In both isomers considered here the nitro-group plane is nearly orthogonal to the mean plane through atoms C(1), C(4), C(5), N(1) and N(2), the corresponding dihedral angle ranging between 72–87° (Table 5). In fact the structures of nitrimines could be roughly split into 'planar' and 'orthogonal', according to the extent of rotation of the nitro group. As has already been pointed out,[10] the 'orthogonal' conformation prevents the conjugation between the nitro group and the imine bond; even in the present cases, the average bond distances for C(5)=N(1) and N(1)–N(2) (1.27 and 1.45 Å, respectively) are in full agreement with standard experimental values for a non-conjugated C=N double bond (1.28 Å)[11] and for an N–N single bond (1.46 Å, from X-ray diffraction;[11] 1.44 ± 4 Å[12]). The amplitude of the O–N–O bond angle seems also to be related to the conformation of the nitrimine substituent, ranging from 120–122° in 'planar' conjugated compounds[13] and between 126–129° in 'orthogonal' derivatives.[3,10] Corresponding values found in the present study range between 127–130°.

The geometry of the rigid cineole skeleton does compare well with that found in a previous determination.[14] Most of the intermolecular contacts in both crystal structures **4** and **5** are in the normal range, only a few being shorter (by 0.15–0.32 Å) with respect to the sum of the involved atoms' van der Waals radii.[15]

Theoretical Calculations.—To compare the geometry found for the two isomers in the crystal state with that of the corresponding isolated molecules, semi-empirical MO calculations[16] were performed on the molecules **4A**, **4B** (Fig. 1) and **5**, using AM1 parameters.[17] In all cases, the final experimental geometry was employed as the starting point for a full optimization, with the keyword PRECISE in order to improve the convergence criteria. Results on geometrical parameters are included in Tables 3–5. The agreement between observed and calculated geometries is fairly good, the discrepancies concerning mainly the nitrimine chain, as expected. In particular, whereas the calculated values for the large R–C=N bond angle (131–132°) are within 2–3° of the observed geometry, the C=N–N bond angles show an increase (by 8–9°) with respect to the corresponding experimental values. Moreover, for compound **5** the calculation leads to an appreciable increase (by 14°) of the dihedral angle between the mean plane of the imine moiety and that of the nitro group (see Table 5). However, the calculated value is near to the dihedral angle observed for **4**, and both the discrepancies noticed here could be due to the packing forces in the crystal state.

The total energies calculated after full optimization differ to within 0.5 kcal mol^{-1}.†

Reactions of Nitrimine **3** *with other Nucleophiles.*—Some reactions of bromonitrimine **3** with nucleophiles were carried out in order to determine the reactivity of the bromine atom and/or the nitrimino group (Scheme 2). As a first nucleophilic reagent we chose hydroxylamine. With excess of hydroxylamine hydrochloride, but in the presence of a *ca.* equimolecular amount of sodium hydroxide with respect to substrate **3** and by working at room temperature, we found that the bromonitrimine **3** reacted only with its nitrimino group, to give the bromoxime **6** in 98% yield. When an excess (>3 mol equiv.) of free hydroxylamine reacted with substrate **3** at room temperature, the reactive 5-bromine atom was also substituted to afford the hydroxyamino oxime **7** in 93% yield. In this compound the 5-proton has the same configuration as in the starting nitrimine **3**, as was shown by the ^1H NMR doublet at δ_H 4.29 (J 4 Hz), which unequivocally means that the hydroxylamino substituent has the same configuration as that of the starting bromine atom.

Finally, when the reaction of substrate **3** with hydroxylamine

* The average value and the range of the considered bond angles have been determined from 16 observations for the nitrimine derivatives in the Crystal Structural Database V4.2 (1990).[9] The database was accessed through 'Servizio Italiano Diffusione Dati Cristallografici del C.N.R.', University of Parma.

† 1 cal. = 4.184 J.

Table 3. Selected bond lengths (Å).[a]

	4			Average of calculated values (see text)
	Mol. A	Mol. B	5	
C(1)–O(1)	1.45	1.44	1.44	1.43
C(2)–O(1)	1.47	1.44	1.46	1.44
C(5)–N(1)	1.28	1.26	1.27	1.29
N(1)–N(2)	1.46	1.43	1.45	1.41
N(2)–O(2)	1.21	1.20	1.19	1.20
N(2)–O(3)	1.21	1.20	1.20	1.20

[a] E.s.d.s range between 0.007–0.017 Å for compound **4**, and between 0.005–0.009 Å for compound **5**.

Table 4. Selected bond angles (°).[a]

	4				
	Exp.			5	
	Mol. A	Mol. B	Calc.	Exp.	Calc.
C(4)–C(5)–N(1)	114.7	115.4	117.4	132.4	130.8
C(1)–C(5)–N(1)	133.4	134.9	131.6	116.1	118.3
C(5)–N(1)–N(2)	117.7	117.8	126.6	120.2	128.1
N(1)–N(2)–O(2)	113.9	116.6	118.0	115.9	117.9
N(1)–N(2)–O(3)	115.8	115.7	118.5	116.5	118.4
O(2)–N(2)–O(3)	129.7	127.2	123.2	126.9	123.1
C(1)–O(1)–C(2)	116.1	116.2	113.7	115.3	113.8

[a] E.s.d.s range between 0.4–1.0° in compound **4**, and between 0.2–0.5° in compound **5**.

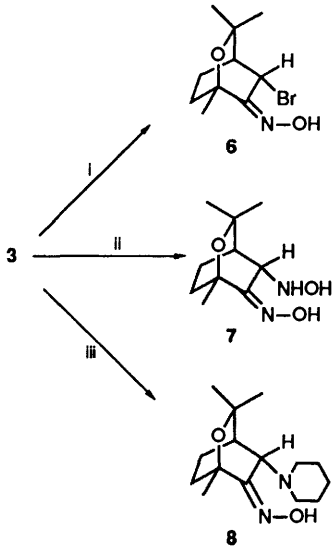
Table 5. Dihedral angles (°) between weighted least-squares planes.

Plane	Through the atoms
1	C(1), C(2), C(3), O(1), C(10)
2	C(1), C(3), C(6), C(7)
3	C(1), C(3), C(4), C(5)
4	C(1), C(4), C(5), N(1), N(2)
5	N(1), N(2), O(2), O(3)

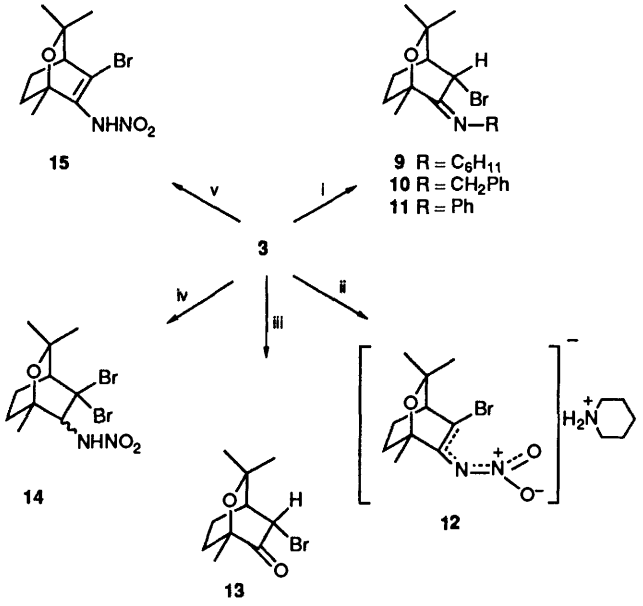
	4			5	
	Exp.				
Planes	Mol. A	Mol. B	Calc.	Exp.	Calc.
1–2	121.4	124.7	121.3	120.5	121.4
1–3	119.2	119.6	121.2	119.4	121.2
4–5	86.9	84.5	82.0	71.7	85.5

hydrochloride was carried out in the presence of excess of piperidine, the 5-(piperidin-1-yl) oxime **8** was obtained in 65% yield. This compound shows not only the usual substitution of the nitrimino group with the hydroxyimino moiety, but also the replacement of the 5-bromine atom by the piperidin-1-yl group, which in the product has the same configuration as that of the starting bromine atom (doublet for 5-H at δ_H 3.64, J 4 Hz). These stereospecific substitutions at C-5 could be tentatively explained by an S_N1 substitution with attack of the carbocation by the nucleophile from the less hindered side of the molecule.

Other reactions we have tried with **3** concerned only the nitrimino group (Scheme 3). Unlike 3-*endo*-bromocamphor nitrimine, which reacted satisfactorily only with aniline,[1] the bromonitrimine **3** reacted smoothly both with aliphatic and with aromatic primary amines to give in 68–81% yield the *N*-substituted imines **9–11**. Heating of compound **3** with secondary aliphatic amines such as pyrrolidine gave a complex mixture of products which could not be characterized.



Scheme 2. *Reagents:* i, $\overset{+}{N}H_3OHCl^-$–NaOH; ii, excess of $\overset{+}{N}H_3OHCl^-$–NaOH; iii, $\overset{+}{N}H_3OHCl^-$–piperidine.



Scheme 3. *Reagents:* i, RNH_2; ii, piperidine; iii, aq. pyridine; iv, $NaBH_3CN$; v, KOH, then 0.75 mol dm^{-3} HCl.

In an ice-cold diethyl ether solution, piperidine afforded, on reaction with compound **3**, the stable salt **12** in 98% yield.

The C=N bond of the nitrimino group could be easily hydrolysed with a mixture of pyridine and water to give, in 83% yield, the already known[18] bromo ketone **13** or reduced with sodium cyanoborohydride to afford the nitramine **14** in 86% yield.

Finally, consecutive treatment of nitrimine **3** with potassium hydroxide and then with aq. hydrochloric acid did not restore the starting compound but gave instead, in high yield, the less stable isomer, namely the *N*-nitro enamine **15**, a feature already observed in a few examples of hindered aliphatic nitrimines.[19]

Experimental

M.p.s were determined with a Fisher-Johns apparatus and are uncorrected. IR spectra were measured with a Perkin-Elmer 398 spectrophotometer. ^1H NMR spectra were recorded on a Hitachi Perkin-Elmer R-600 instrument (60 MHz), and ^{13}C NMR spectra on a Varian FT-80 apparatus (80 MHz), with tetramethylsilane as internal standard. Ether refers to diethyl ether. Light petroleum refers to the fraction boiling in the range 40–70 °C.

(1S,4S,5S)-5-*Bromo*-1,3,3-*trimethyl*-N-*nitro*-2-*oxabicyclo*-[2.2.2]*octan*-6-*imine* **3**.—1,3,3-Trimethyl-*N*-nitro-2-oxabicyclo-[2.2.2]octan-6-imine **1**[6] (63.7 g, 0.30 mol) was dissolved in warm dichloromethane (95 cm^3), and the solution was diluted with dry ethanol (45 cm^3) and cooled. In the same way, a solution of potassium hydroxide (19.1 g, 0.34 mol) in dry ethanol (130 cm^3) was prepared and added at once to the above, vigorously stirred solution. The precipitated potassium salt **2** was dissolved by the addition of water (95 cm^3) and the cold solution was added dropwise to a cooled (−5 °C), stirred solution of bromine (15.5 cm^3, ~0.30 mol) in acetic acid (60 cm^3). The mixture was stirred for 5 min, and then decolourized with 5% aq. sodium hydrogen sulphite and extracted thoroughly with ether. The extracts were washed with saturated aq. $NaHCO_3$, dried ($MgSO_4$), and evaporated under reduced pressure to yield TLC pure *bromonitrimine* **3** (75.1 g, 86%), $[\alpha]_D^{20}$ +361.4° (*c* 3, $CHCl_3$); m.p. 135–136 °C (from ether) (Found: C, 41.1; H, 5.3; N, 9.8; Br, 27.4. $C_{10}H_{15}BrN_2O_3$ requires C, 41.2; H, 5.2; N, 9.6; Br, 27.6%); ν_{max}(KBr) 1630 (C=N), 1575 (NNO_2), and 1320 cm^{-1} (NNO_2); δ_H ($CDCl_3$) 1.30 (6 H, s, 2 × Me), 1.45 (3 H, s, Me), 1.7–2.3 (5 H, m, 2 × CH_2 and 4-H), and 5.52 (1 H, d, *J* 4 Hz, 5-H); δ_C($CDCl_3$) 173.83 (s, C=N), 74.94 and 73.12 (2 s, C-1 and C-3), 42.22 and 39.28 (2 d, C-4 and C-5), 29.04 (q, Me), 28.28 (m, C-7), 27.71 (q, Me), 21.27 (q, Me), and 16.83 (m, C-8).

(1S,4S)-5,5-*Dibromo*-1,3,3-*trimethyl*-N-*nitro*-2-*oxabicyclo*-[2.2.2]*octan*-6E-*imine* **4**.—An alkaline solution of nitrimine **3** potassium salt, prepared by addition of compound **3** (8.0 g, 27.5 mmol) in ether (35 cm^3) and methanol (20 cm^3) to a solution of potassium hydroxide (1.68 g, 30 mmol) in methanol (40 cm^3), was added in 5 min to a stirred, cooled (−5 °C) solution of bromine (1.45 cm^3, ~28 mmol) in acetic acid (15 cm^3). The mixture was stirred for 3 min, water (150 cm^3) was added, and excess of bromine was destroyed with 5% aq. sodium hydrogen sulphite. The precipitate was extracted with ether, and the extracts were washed five times with saturated aq. $NaHCO_3$, dried ($MgSO_4$), and evaporated under reduced pressure at 35–40 °C to give translucent crystals, which were recrystallized from ether–light petroleum (1:1) to afford (E)-*dibromonitrimine* **4** (8.5 g, 83%), $[\alpha]_D^{22}$ +190.8° (*c* 2.6, benzene), m.p. 89–90 °C* (Found: C, 32.6; H, 3.8; N, 7.8; Br, 43.2. $C_{10}H_{14}Br_2N_2O_3$ requires C, 32.5; H, 3.8; N, 7.6; Br, 43.2%); ν_{max}(KBr) 1630 (C=N), 1570 (NNO_2), and 1310 cm^{-1} (NNO_2); δ_H($CDCl_3$) 1.44 (3 H, s, Me), 1.49 (3 H, s, Me), 1.70 (3 H, s, Me), and 1.8–2.8 (5 H, m, 2 × CH_2 and 4-H); δ_C($CDCl_3$) 173.71 (s, C=N), 77.75 and 76.88 (2 s, C–O–C), 61.04 (s, CBr_2), 53.21 (d, C-4), 34.20 (q, Me), 32.85 (q, Me), 31.04 (m, C-7), 25.09 (m, C-8), and 22.32 (q, Me).

(1S,4S)-5,5-*Dibromo*-1,3,3-*trimethyl*-N-*nitro*-2-*oxabicyclo*-[2.2.2]*octan*-6Z-*imine* **5**.—(i) *From the mixture of isomers.* Bromine (6.5 cm^3, ~0.126 mol) was slowly added to a cooled (−5 °C), stirred solution of salt **2**, prepared by addition of compound **1** (5.94 g, 28 mmol) in methanol (60 cm^3) to a solution of potassium hydroxide (10.2 g, 0.182 mol) in methanol (50 cm^3). The mixture was stirred for 5 min, water (200 cm^3) was added, and excess of bromine was destroyed with sodium hydrogen sulphite. The precipitate, a mixture of imines **4** and **5**, was filtered, air dried (6.3 g, 61%), and dissolved in chloroform (70 cm^3). The solution was stirred at room temperature for a week and evaporated under reduced pressure. The residue was chromatographed on Florisil with ether as eluant to afford (Z)-*dibromonitrimine* **5** (5.8 g, 92%), $[\alpha]_D^{22}$ +243.7° (*c* 2.6, benzene); m.p. 118–120 °C (decomp.)† [from ether–light petroleum (1:1)] (Found: C, 32.4; H, 3.7; N, 7.6; Br, 43.3%); ν_{max}(KBr) 1625 (C=N), 1575 (NNO_2), and 1310 cm^{-1} (NNO_2); δ_H($CDCl_3$) 1.35 (3 H, s, Me), 1.50 (3 H, s, Me), 1.61 (3 H, s, Me), and 1.8–2.8 (5 H, m, 2 × CH_2 and 4-H); δ_C($CDCl_3$) 165.96 (s, C=N), 77.08 and 75.77 (s and t, C–O–C plus $CDCl_3$), 53.50 (d, C-4), 48.98 (s, CBr_2), 31.79 (q, Me), 31.51 (q, Me), 28.76 (m, C-7), 23.97 (m, C-8), and 22.16 (q, Me).

(ii) *By conversion of the isomer* **4**. A solution of *E*-imine **4** (3.7 g, 10 mmol) in chloroform (40 cm^3) was stirred for six days at room temperature. The solvent was evaporated off under reduced pressure, and the residue was chromatographed on Florisil with ether as eluant and recrystallized from ether–light petroleum (1:1) to give the isomer **5** (3.15 g, 85% conversion), m.p. 118–120 °C (decomp.).

CAUTION: Refluxing of compound **4** in toluene solution did not afford the above conversion owing to a remarkable decomposition, whereas rapid heating in a Petri dish caused a **violent explosion** with formation of a black tarry residue.

(1S,4S,5S)-5-*Bromo*-N-*hydroxy*-1,3,3-*trimethyl*-2-*oxabicyclo*-[2.2.2]*octan*-6-*imine* **6**.—Hydroxylamine hydrochloride (5.0 g, 72 mmol) and sodium hydroxide (2.3 g, 57.5 mmol) were added to methanol (40 cm^3) and the mixture was stirred at room temperature for 10 min. The precipitate was filtered off and the solution was added during *ca.* 1 h to a stirred, ice-cooled solution of compound **3** (16.0 g, 55 mmol) in ether (130 cm^3) containing suspended hydroxylamine hydrochloride (1.0 g, 14.5 mmol). The mixture was stirred at room temperature for 2 h, and then diluted with water (50 cm^3), and the organic layer was separated, washed with water (50 cm^3), dried ($MgSO_4$), and evaporated under reduced pressure to give the *bromo oxime* **6** (14.2 g, 98%), m.p. 174–175 °C [from ether–light petroleum (9:1)] (lit.,[20] 165 °C) (Found: C, 46.0; H, 6.2; N, 5.5. Calc. for $C_{10}H_{16}BrNO_2$: C, 45.8; H, 6.1; N, 5.5%); ν_{max}(KBr) 3310 (OH) and 1650 cm^{-1} (C=N); δ_H[$(CD_3)_2SO$] 1.06 (3 H, s, Me), 1.18 (3 H, s, Me), 1.28 (3 H, s, Me), 1.5–2.2 (4 H, m, 2 × CH_2), 3.40 (1 H, br s, 4-H), 5.28 (1 H, d, *J* 4 Hz, 5-H), and 11.52 (1 H, s, OH; disappears with CF_3CO_2D).

(1S,4R,5S)-5-*Hydroxyamino*-N-*hydroxy*-1,3,3-*trimethyl*-2-*oxabicyclo*[2.2.2]*octan*-6-*imine* **7**.—A solution of bromonitrimine **3** (5.82 g, 20 mmol) in dichloromethane (15 cm^3)–methanol (20 cm^3) was slowly added to a mixture of hydroxylamine hydrochloride (8.0 g, 0.115 mol) and sodium hydroxide (2.8 g, 70 mmol) in methanol (50 cm^3) previously stirred for 10 min. The mixture was stirred for 6 h at room temperature, filtered, the solution was evaporated under reduced pressure, and the residue was treated with water (25 cm^3) and extracted thoroughly with ether. The extracts were dried ($MgSO_4$) and evaporated to give a viscous oil which crystallized on addition of a little light petroleum–ether (7:1). The *hydroxyamino oxime* **7** was obtained as white crystals (4.0 g, 93%), m.p. 152–153 °C (from ether) (Found: C, 55.9; H, 8.5; N, 12.9. $C_{10}H_{18}N_2O_3$ requires C, 56.1; H, 8.5; N, 13.1%); ν_{max}(KBr) 3500 (OH) and 3240 cm^{-1} (OH); δ_H[$(CD_3)_2SO$] 1.10 (6 H, s,

* After melting had occurred, the liquid solidified at 100–105 °C upon a slow increase of the temperature (2–3 °C min^{-1}) and then melted at 113–115 °C with decomposition.

† The m.p. can vary from 115–117 °C (slow heating) to 123–124 °C (rapid heating).

2 × Me), 1.25 (3 H, s, Me), 4.29 (1 H, d, *J* 4 Hz, 5-H), 6.20 (1 H, br s, NH; disappears with CF_3CO_2D), 7.38 (1 H, s, NHOH; disappears with CF_3CO_2D), and 11.0–11.5 (1 H, very br s, =NOH; disappears with CF_3CO_2D); this signal is visible only in dilute solutions, probably owing to a chelation effect.

(1S,4R,5S)-N-*Hydroxy*-1,3,3-*trimethyl*-5-(*piperidin*-1-*yl*)-2-*oxabicyclo*[2.2.2]*octan*-6-*imine* **8**.—A solution of compound **3** (20.0 g, 69 mmol) in dry ethanol (150 cm^3) was added dropwise to a stirred mixture of hydroxylamine hydrochloride (6.0 g, 86 mmol) and piperidine (18.0 g, 0.211 mol) in dry ethanol (90 cm^3) heated at 55–60 °C on a steam-bath. The mixture was heated for a further 5 min, ethanol and excess of piperidine were removed under reduced pressure, and the residue was treated with water (200 cm^3) and extracted thoroughly with ether. The extracts were dried ($MgSO_4$), concentrated, and chromatographed on Florisil with ether as eluant to yield the *piperidino oxime* **8** as white crystals (12.0 g, 65%), m.p. 112 °C [from light petroleum–ether (9:1)] (Found: C, 67.8; H, 9.9; N, 10.6. $C_{15}H_{26}N_2O_2$ requires C, 67.6; H, 9.8; N, 10.5%); $\nu_{max}(CHCl_3)$ 3500–3200 (OH) and 1630 cm^{-1} (C=N); $\delta_H[(CD_3)_2SO]$ 1.00 (3 H, s, Me), 1.17 (3 H, s, Me), 1.20 (3 H, s, Me), 1.3–2.1 (11 H, m, 5 × CH_2 and 4-H), 2.52 (4 H, br s, 2 × CH_2N), 3.64 (1 H, d, *J* 4 Hz, 5-H), and 11.90 (1 H, s, OH; disappears with CF_3CO_2D).

General Procedure for the Preparation of N-*Substituted* (1S,4S,5S)-5-*Bromo*-1,3,3-*trimethyl*-2-*oxabicyclo*[2.2.2]*octan*-6-*imines* **9–11**.—Bromonitrimine **3** (2.0 g, 7 mmol) was added in small portions to a solution of a primary amine (8.5 mmol) in dry toluene (40 cm^3) and the resulting solution was heated and stirred at 70–80 °C (steam-bath) for 10 min (15 min in the case of aniline). The solvent was removed under reduced pressure, the residue was treated with water (100 cm^3), acidified with 0.5 mol dm^{-3} HCl (pH 2–3), and extracted thoroughly with ether. The extracts were dried ($MgSO_4$), evaporated under reduced pressure, and the residue was chromatographed on neutral alumina (grade I) with ether as eluant to yield a white solid, which was recrystallized from a suitable solvent to give the following products.

(1S,4S,5S)-5-*Bromo*-N-*cyclohexyl*-1,3,3-*trimethyl*-2-*oxabicyclo*[2.2.2]*octan*-6-*imine* **9** (78%), m.p. 99–100 °C (from ether) (Found: C, 58.8; H, 8.1; N, 4.5. $C_{16}H_{26}BrNO$ requires C, 58.5; H, 8.0; N, 4.3%); ν_{max}(KBr) 1670 cm^{-1} (C=N); $\delta_H(CDCl_3)$ 1.17 (3 H, s, Me), 1.22 (3 H, s, Me), 1.38 (3 H, s, Me), 1.5–2.3 (15 H, m, 7 × CH_2 and 4-H), 3.6–4.0 (1 H, m, CHN), and 5.05 (1 H, d, *J* 4 Hz, 5-H).

(1S,4S,5S)-N-*Benzyl*-5-*bromo*-1,3,3-*trimethyl*-2-*oxabicyclo*-[2.2.2]*octan*-6-*imine* **10** (81%), m.p. 78–80 °C (from light petroleum) (Found: C, 61.0; H, 6.6; N, 4.1. $C_{17}H_{22}BrNO$ requires C, 60.7; H, 6.6; N, 4.2%); ν_{max}(KBr) 1660 cm^{-1} (C=N); $\delta_H(CDCl_3)$ 1.10 (3 H, s, Me), 1.30 (3 H, s, Me), 1.38 (3 H, s, Me), 1.8–2.3 (5 H, m, 2 × CH_2 and 4-H), 4.63 and 4.93 (2 H, ABq, *J* 14 Hz, CH_2Ph), 5.07 (1 H, d, *J* 4 Hz, 5-H), and 7.2–7.6 (5 H, m, Ph).

(1S,4S,5S)-5-*Bromo*-1,3,3-*trimethyl*-N-*phenyl*-2-*oxabicyclo*-[2.2.2]*octan*-6-*imine* **11** (68%), m.p. 64–65 °C (from light petroleum) (Found: C, 59.6; H, 6.2; N, 4.2. $C_{16}H_{20}BrNO$ requires C, 59.6; H, 6.3; N, 4.3%); ν_{max}(KBr) 1670 (C=N) and 1600 cm^{-1} (Ph); $\delta_H(CDCl_3)$ 1.30 (3 H, s, Me), 1.36 (3 H, s, Me), 1.42 (3 H, s, Me), 1.7–2.3 (5 H, m, 2 × CH_2 and 4-H), 5.16 (1 H, d, *J* 4 Hz, 5-H), and 6.7–7.4 (5 H, m, Ph).

Preparation of the Salt **12** *from the Bromonitrimine* **3** *and Piperidine*.—A solution of piperidine (0.94 g, 11 mmol) in anhydrous ether (20 cm^3) was added to an ice-cooled solution of compound **3** (2.91 g, 10 mmol) in the same solvent (60 cm^3). The mixture was stirred for 10 min, ether was evaporated off, and the white solid residue was washed with light petroleum and dried to afford the *salt* **12** (3.69 g, 98%), m.p. 133–138 °C (decomp.) (Found: C, 47.8; H, 6.9; N, 11.3. $C_{15}H_{26}BrN_3O_3$ requires C, 47.9; H, 7.0; N, 11.2%); ν_{max}(KBr) 3100–2300 ($\overset{+}{N}H_2$), 1635 (C=N), and 1600 cm^{-1} (conjugated C=C); $\delta_H(CDCl_3)$ 1.15 (3 H, s, Me), 1.28 (3 H, s, Me), 1.34 (3 H, s, Me), 1.5–2.2 (10 H, m, 5 × CH_2), 2.58 (1 H, br s, 4-H), 3.0–3.4 (4 H, m, 2 × CH_2N), and 8.85 (2 H, br s, $\overset{+}{N}H_2$; disappears with D_2O).

(1S,4S,5S)-5-*Bromo*-1,3,3-*trimethyl*-2-*oxabicyclo*[2.2.2]*octan*-6-*one* **13**.—Bromonitrimine **3** (1.5 g, 5.15 mmol) was dissolved in a mixture of pyridine (6 cm^3) and water (1 cm^3), the solution was heated at 50–60 °C for one hour, then evaporated under reduced pressure, and the residue was extracted with ether. The extracts were washed with 1 mol dm^{-3} HCl, dried ($MgSO_4$), concentrated, and chromatographed on Florisil with ether as eluant to give the bromo ketone **13** (1.06 g, 83%), m.p. 94–95 °C (from light petroleum) (lit.,[18] 93.5–94.5 °C); $\delta_H(CDCl_3)$ 1.21 (3 H, s, Me), 1.35 (3 H, s, Me), 1.48 (3 H, s, Me), 1.6–2.4 (5 H, m, 2 × CH_2 and 4-H), and 5.00 (1 H, d, *J* 2 Hz, 5-H).

(1S,4S,5S)-5-*Bromo*-1,3,3-*trimethyl*-N-*nitro*-2-*oxabicyclo*-[2.2.2]*octan*-6-*amine* **14**.—Sodium cyanoborohydride (2.76 g, 44 mmol) was added portionwise (~0.4 g every 10 min) to a stirred, ice-cooled solution of compound **3** (2.91 g, 10 mmol) in methanol (60 cm^3). After the mixture had been stirred for 20 min at room temperature, the solvent was evaporated off under reduced pressure, the residue was treated with water (90 cm^3) and the solution was washed with ether. The aq. solution was acidified with 1 mol dm^{-3} HCl (pH ~ 0) and extracted thoroughly with ether. The extracts were dried ($MgSO_4$), concentrated, and chromatographed on Florisil with ether as eluant to afford the *bromo nitramine* **14** as a white solid (2.5 g, 86%), m.p. 137–139 °C [from ether–light petroleum (2:1)] (Found: C, 41.1; H, 5.6; N, 9.7. $C_{10}H_{17}BrN_2O_3$ requires C, 41.0; H, 5.8; N, 9.6%); ν_{max}(KBr) 3320 (NH), 1575 and 1355 cm^{-1} (NO_2); $\delta_H[(CD_3)_2SO]$ 1.05 (3 H, s, Me), 1.27 (6 H, s, 2 Me), 1.7–2.2 (5 H, m, 2 × CH_2 and 4-H), 4.2–4.6 (1 H, m, 6-H), 5.30 (1 H, d, *J* 9 Hz, 5-H), and 12.60 (1 H, br s, NH; disappears with CF_3CO_2D).

(1S,4S)-5-*Bromo*-1,3,3-*trimethyl*-N-*nitro*-2-*oxabicyclo*[2.2.2]-*oct*-5-*en*-6-*amine* **15**.—A cold solution of potassium hydroxide (0.595 g, 10.6 mmol) in methanol (15 cm^3) was added all at once to a solution of the nitrimine **3** (2.91 g, 10 mmol) in dichloromethane (15 cm^3). The resulting solution was vigorously stirred for 3 min, and then concentrated under reduced pressure at 55–65 °C, and the liquid residue was diluted with water (40 cm^3) and extracted with ether (50 cm^3). The extracts were washed with water (20 cm^3) which was added to the previous aq. phase. The collected water solutions were acidified with 0.75 mol dm^{-3} HCl (40 cm^3) and extracted thoroughly with ether–light petroleum (4:1). The extracts were dried ($MgSO_4$), and evaporated under reduced pressure at 40–50 °C to give TLC–pure N-*nitro enamine* **15** (2.6 g, 89%), $[\alpha]_D^{20}$ −65.3° (*c* 3, $CHCl_3$), m.p. 103–105 °C [from light petroleum–ether (2:1)] (Found: C, 41.1; H, 5.2; N, 9.6. $C_{10}H_{15}BrN_2O_3$ requires C, 41.2; H, 5.2; N, 9.6%); $\nu_{max}(CHCl_3)$ 3370 (NH), 1635 (C=C), 1585 (NO_2), and 1330 cm^{-1} (NO_2); $\delta_H(CDCl_3)$ 1.13 (3 H, s, Me), 1.40 (3 H, s, Me), 1.74 (3 H, s, Me), 1.5–2.3 (4 H, m, 2 × CH_2), 2.80 (1 H, br s, 4-H), and 9.84 (1 H, br s, NH; disappears with D_2O); $\delta_C(CDCl_3)$ 137.80 and 128.64 (2 s, C=C), 78.58 and 77.30 (2 s, C–O–C), 53.11 (d, C-4), 33.78 (m, C-7), 30.13 (q, Me), 28.91 (q, Me), 22.70 (q, Me), and 22.03 (m, C-8).

Crystal Data.—Compound **4**, m.p. 89–90 °C; $C_{10}H_{14}Br_2N_2O_3$, M = 370.04, orthorhombic, *a* = 7.732(4), *b* = 11.657(4), *c* = 29.427(8) Å, *V* = 2652 $Å^3$, space group $P2_12_12_1$, *Z* = 8,

D(calc.) = 1.853 g cm^{-3}, μ(Mo-Kα) = 6.05 mm^{-1}, F(000) = 1456, crystal dimensions 0.38 × 0.40 × 0.40 mm.

Compound **5**, m.p. 118–120 °C (decomp.); $C_{10}H_{14}Br_2N_2O_3$, M = 370.04, orthorhombic, a = 6.685(3), b = 13.584(3), c = 14.465(4) Å, V = 1314 Å^3, space group $P2_12_12_1$, Z = 4, D(calc.) = 1.871 g cm^{-3}, μ(Mo-Kα) = 6.11 mm^{-1}, F(000) = 728, crystal dimensions 0.38 × 0.40 × 0.42 mm.

Data Collection and Processing.—The diffraction data were collected by means of a CAD-4 diffractometer with Mo-Kα radiation (λ = 0.7107 Å, graphite monochromator) in the range $2.5 \leqslant \theta \leqslant 25°$ for compound **4**, $2.5 \leqslant \theta \leqslant 27.5°$ for compound **5** with ω–θ scan mode; immediately after each reflection the corresponding Friedel opposite was measured. For each compound eight reflections were used to control the orientation every 200 reflections, and two to test the crystal stability every 3600 s. Other parameters and data: compound **4**, scan width 1.35°, variable scan speed between 1.0–6.7° min^{-1}, 4649 independent reflections of which 3178 with $F \geqslant 3\sigma(F)$; for compound **5**, scan width 1.28°, variable scan speed between 1.3–5.2° min^{-1}, 2996 independent reflections of which 2308 with $F \geqslant 3\sigma(F)$. Corrections for decay (overall, 24% for compound **4** and 12% for compound **5**), Lorentz, polarization and absorption effects (see below) were applied.

Structure Determination and Refinement.—Both structures were solved by Patterson and Fourier methods. After some isotropic cycles, an empirical absorption correction was applied;[21] the maximum and minimum absorption correction factors were 1.078 and 0.704 respectively for compound **4**, 1.158 and 0.701 respectively for compound **5**. Then refinement was resumed by anisotropic full-matrix least-squares using the SHELX 76 program and the complex scattering factors included therein.[22] The same weighting scheme, $w = [\sigma^2(F) + 0.001F^2]^{-1}$, was adopted for both isomers. The hydrogen atoms were located in calculated positions at 0.95 Å from the bonded carbon atom and were not refined. At the end of the least-squares process, the co-ordinates for methyl hydrogen atoms were slightly modified by rotating the methyl groups around the C–C axis, to achieve a minimum in the potential energy.[23] A thermal factor U(iso) equal to 1.2 times the U(eq) of the bonded carbon atom was assigned to every hydrogen atom. For each isomer the last part of the refinement was repeated on the inverted structure using the same data set. This allowed the absolute configuration to be determined; in both cases it corresponded to the configuration opposite to that obtained from the structure solution. The final discrepancy indexes $R = \Sigma||\Delta F|/\Sigma|F_o||$, $R_w = [\Sigma w(\Delta F)^2/\Sigma wF_o^2]^{\frac{1}{2}}$ and the goodness of fit $S = [\Sigma(w\Delta F^2)/(N - P)]^{\frac{1}{2}}$ are 0.041, 0.049 and 1.052 respectively for compound **4** over 3178 observed reflections (enantiomer: 0.058, 0.072, 1.798), and 0.033, 0.041 and 0.915 for compound **5** over 2308 observed reflections (enantiomer: 0.050, 0.063, 1.524). The results presented in this paper refer to the correct absolute configuration for both compounds. All geometrical calculations were carried out using the program PARST.[24]

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