J. Org. Chem. **1996,** *61,* 451−454

Structure Determination of the Products from the Acid-Catalyzed Condensation of Indole with Acetone[†]

Wayland E. Noland,* Michael J. Konkel, Lisa M. C. Konkel, and Bradley C. Pearce

Department of Chemistry, University of Minnesota, 207 Pleasant Street, S.E.,
Minneapolis, Minnesota 55455

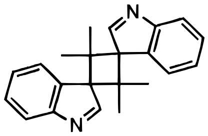
Charles L. Barnes and Elmer O. Schlemper[‡]

College of Arts and Sciences, Department of Chemistry, University of Missouri—Columbia, 123 Chemistry
Building, Columbia, Missouri 65211

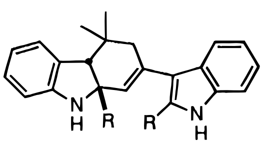
Received September 1, 1995[⊗]

Four of the previously reported compounds obtained from the acid-catalyzed condensation of indole with acetone are now assigned the following structures: *cis*-4,4a,9,9a-tetrahydro-2-(1*H*-indol-3-yl)-4,4-dimethyl-3*H*-carbazole (**2a**), 1,1′,4,4′-tetrahydro-1,1,1′,1′-tetramethyl-3,3′(2*H*,2′*H*)-spirobi[cyclopent[*b*]indole] (**4**), 4,4a-dihydro-2-(3-1*H*-indolyl)-4,4-dimethyl-3*H*-carbazol-4a-ol (**7**), and 5-(2-aminophenyl)-1,3,4,5-tetrahydro-1,1,4,4-tetramethylcyclopent[*kl*]acridine (**8**). The structure of the novel rearrangement product **8** was solved by an X-ray crystal structure determination. The two previously reported autoxidation products of **4** are now assigned the following structures: 1,3′,4,4′-tetrahydro-1,1,4′,4′-tetramethyl-*cis*-dispiro[cyclopent[*b*]indole-3(2*H*),2′(5′*H*)-furan-5′,3″-[3*H*]-indol]-2″(1″*H*)-one (**5**) and 1,4-dihydro-1,1,5′,5′-tetramethylspiro[cyclopent[*b*]indole-3(2*H*),3′(4′*H*)-1-benzazocine]-2′(1′*H*),6′(5′*H*)-dione (**6**).

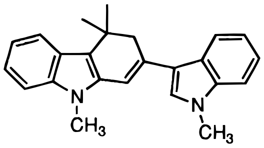
In 1913 Scholtz[1] reported that the hydrochloric acid-catalyzed condensation of indole with acetone gave a monobase to which he assigned structure **1**. We found that this reaction gives a complex mixture of products,[2] including one that matches Scholtz's compound in empirical formula, melting point, and color. We assigned structure **2a** to this compound, although the location of the double bond (1,2- or 2,3-position) in the tetrahydrocarbazole was uncertain at that time. At the same time,[3] an analogous compound (**2b**) was isolated from this reaction when 2-methylindole, instead of indole, was used. More recently, we have determined the position of the double bond (by NMR spectroscopy) to be that shown in the tetrahydrocarbazole **2a**.[4,5] Tetrahydrocarbazole **2a** was previously dehydrogenated and methylated, giving dihydrocarbazole **3**.[2] An independent synthesis of dihydrocarbazole **3** has been carried out.[5] We have also determined from NMR studies that the stereochemistry of tetrahydrocarbazole **2a** is *cis*. Several of the compounds isolated from the same reaction as **2a** were only partially characterized and not assigned structures in the original paper,[2] but are now assigned structures in this paper.



1



2a, R = H
b, R = Me



3

Compound 1 of our earlier paper[2] was described as having an empirical formula $C_{25}H_{26}N_2$, which corresponds to a 2:3 condensation product of indole to acetone with the loss of three molecules of water. We now assign structure **4** to this compound.[4,5] We also reported that compound 1 is easily autoxidized to two compounds with melting points of 230−231 and 175−178 °C, to which we now assign structures **5** and **6**, respectively. Banerji *et al.*[6] also isolated compounds **4** and **5** (along with several other compounds[6,7] which we did not isolate in our studies) from the condensation of indole with acetone catalyzed by boron trifluoride etherate in methylene chloride. The spectral and physical data that we obtained for our compounds matched that which was reported for **4** and **5**, except that the melting point which

---

[†] Paper No. 77 presented before the Organic Division at the 206th ACS National Meeting, Chicago, IL, Aug 22, 1993; Abstract ORGN 77.

[‡] Deceased April 5, 1994.

[⊗] Abstract published in *Advance ACS Abstracts,* January 1, 1996.

(1) Scholtz, M. *Ber. Dtsch. Chem. Ges.* **1913**, *46*, 1082−1089.

(2) Noland, W. E.; Richards, C. G.; Desai, H. S.; Venkiteswaran, M. R. *J. Org. Chem.* **1961**, *26*, 4254−4262.

(3) Noland, W. E.; Venkiteswaran, M. R.; Lovald, R. A. *J. Org. Chem.* **1961**, *26*, 4249−4254.

(4) (a) Pearce, Brad C. A Symmetrical Spiro 2:3 Cyclization Product from the Condensation of Indole with Acetone. Paper presented before Session III (Organic) at the 21st Annual Undergraduate Symposium in Chemistry (sponsored by the Minnesota Section of the American Chemical Society), University of Wisconsin at River Falls, April 28, 1979. (b) In a private communication to Jan Bergman, we disclosed our conclusions concerning this structure. He then published this information[5] while acknowledging our contribution. Our new data for compound **2a** are provided in the Experimental Section.

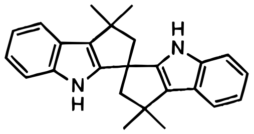
(5) Bergman, J.; Norrby, P.-O.; Tilstam, U.; Venemalm, L. *Tetrahedron* **1989**, *45*, 5549−5564.

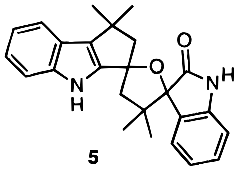
(6) Banerji, J.; Chatterjee, A.; Manna, S.; Pascard, C.; Prangé, T.; Shoolery, J. N. *Heterocycles* **1981**, *15*, 325−336.

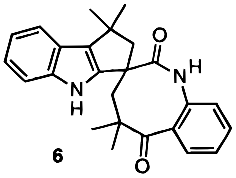
(7) Chatterjee, A.; Manna, S.; Banerji, J.; Pascard, C.; Prangé, T.; Shoolery, J. N. *J. Chem. Soc., Perkins Trans. 1* **1980**, 553−555.

0022-3263/96/1961-0451$12.00/0 © 1996 American Chemical Society

we found for purified **5** (262−263 °C) is considerably higher than that which was previously reported[6] (245 °C). Mixture melting points of our compounds with Banerji *et al.*'s compounds of structures **4** and **5** were intermediate between our samples and theirs, but not depressed. The structure of **4** was supported by NMR studies, and the structure of **5** was confirmed by an X-ray crystallographic structure determination.[6] The oxidation product with assigned structure **6** has a molecular formula, determined by elemental analysis and mass spectrometry, of $C_{25}H_{26}N_2O_2$ (which is isomeric with **5**). The ^1H NMR spectrum shows four methyl singlets at δ 1.20, 1.31, 1.41, and 1.49 ppm. It also shows signals for two sets of geminally coupled protons at 1.88 and 2.94 ppm ($J = 13$ Hz), and at 2.06 and 2.26 ppm ($J = 16.5$ Hz). The ^{13}C NMR spectrum shows, along with others, signals at δ 175.8 and 213.5 ppm. The former chemical shift is consistent with an amide carbonyl and the latter with a ketone carbonyl. All spectroscopic data are consistent with the assigned structure **6**.


4


5


6

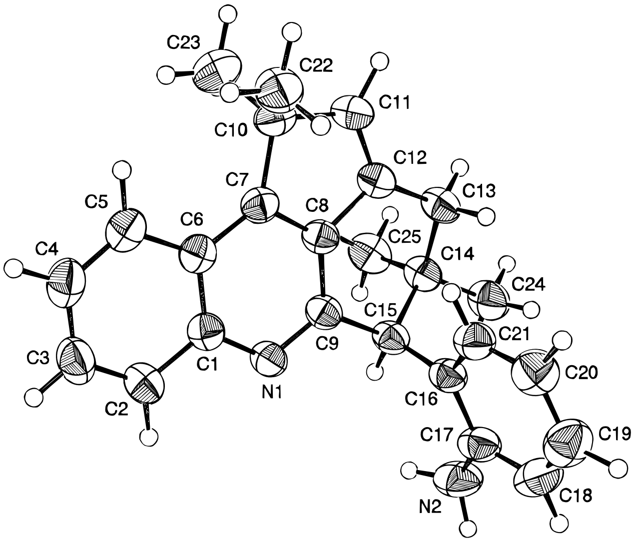
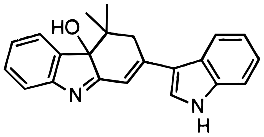
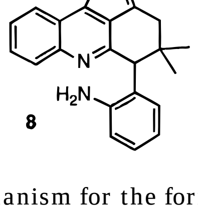


Figure 1. ORTEP drawing of compound **8**.

Compound 2 of our earlier paper was postulated to be an autoxidation product of **2a**, with an empirical formula of $C_{22}H_{20}N_2O$, to which we now assign structure **7**. Mass spectral analysis gave a molecular weight of 328. A ^1H NMR spectrum in DMSO-d_6 shows two methyl singlets at δ 0.53 and 1.44 ppm, a geminally coupled ($J = 17.3$ Hz) pair of doublets at δ 2.54 and 3.08 ppm, a singlet at δ 5.69 ppm, 10 aromatic or olefinic protons from δ 6.93 to 7.93 ppm, and an indole NH at δ 11.68 ppm. At first we thought that the singlet at δ 5.69 ppm was due to a vinyl proton, but a ^1H NMR spectrum obtained at 102 °C showed upfield shifts of 0.35 and 0.38 ppm for the peaks observed at room temperature at δ 5.69 and 11.68, respectively. On this basis, the singlet at δ 5.69 is assigned to a hydroxyl proton. A COSY experiment, which shows allylic coupling of the doublet at δ 3.08 with a finely split singlet at δ 6.93 ppm, does not show any long range coupling with the singlet at δ 5.69. The spectrum does not show any other long range coupling for the singlet at δ 6.93. Therefore, the singlet at δ 6.93 is assigned to the vinyl proton, and the methylene hydrogens at δ 2.54 and 3.08 are allylic. The doublet at δ 3.08 also shows long range coupling to the methyl singlet at δ 0.53 ppm, which, in turn, shows long range coupling to the methyl singlet at δ 1.44 ppm. This supports a structure with a geminal dimethyl group adjacent to the methylene. The structure of **7** is consistent with it being an autoxidation product of **2a**.


7

Compound 3 of our earlier paper[2] was described as having the same empirical formula as compound 1, $C_{26}H_{26}N_2$. Mass spectral analysis confirms this, giving a molecular weight of 354. A ^1H NMR spectrum shows methyl singlets at δ 0.96, 0.99, 1.52, and 1.60 ppm, two geminally coupled protons as doublets at δ 2.30 and 2.60 ppm, a proton as a singlet at δ 4.33 ppm, two protons as a singlet at δ 5.31 ppm, and nine aromatic and olefinic protons from δ 6.17 to 8.12 ppm. Several possible structures seemed to fit the spectroscopic data. Therefore, an X-ray crystallographic structure determination was carried out, and we were surprised to discover that the structure contained a quinoline and an aniline (structure **8**) instead of indole moieties. Figure 1 is an ORTEP[8] drawing of the structure.


8

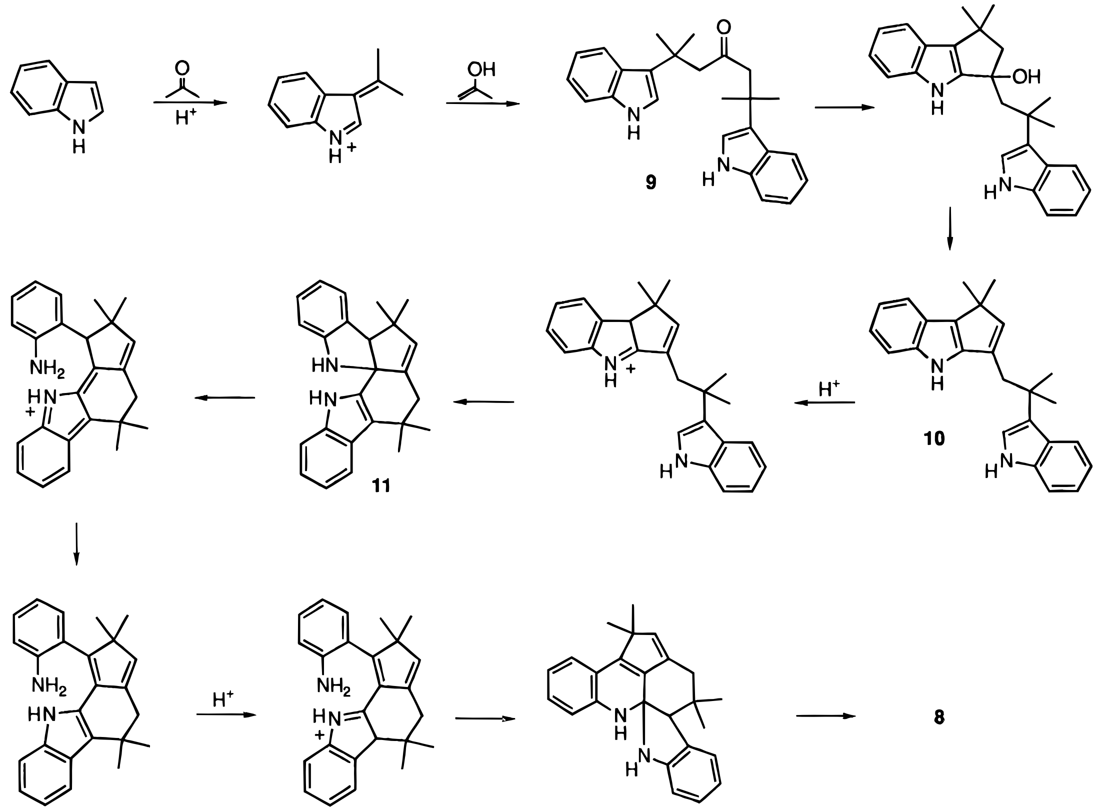
A proposed mechanism for the formation of structure **8** is shown in Scheme 1. Indole condenses with acetone, by one of several possible routes (only one is shown), to form indolyl ketone **9**. Ketone **9** cyclizes,[9] with subse-

---

(8) Johnson, C. K. ORTEP II. Report ORNL-5138; Oak Ridge National Laboratory, TN, 1976.

(9) Electrophilic substitution at the 2-position of 3-alkylindoles has been previously observed. A few examples include: (a) Noland, W. E.; Robinson, D. N. *Tetrahedron* **1958**, *3*, 68−72; (b) St. C. Black, D.; Craig, D. C.; Kumar, N. *J. Chem. Soc., Chem. Commun.* **1989**, 425−426; (c) St. C. Black, D.; Craig, D. C.; Kumar, N. *Tetrahedron Lett.* **1991**, *32*, 1587−1590.

Scheme 1



quent dehydration, to intermediate **10**, which rearranges by an intramolecular nucleophilic attack by the indolyl moiety on the protonated cyclopentindole, giving tetrahydrocarbazole **11**. Intermediate **11** then undergoes a C−N bond cleavage, followed by an intramolecular attack by the intermediate aniline on the protonated indole, giving, after another C−N bond cleavage, tetrahydroacridine **8**.

Experimental Section

General Information. Melting points are uncorrected. The NMR spectra are referenced to the solvent; chemical shifts are given in δ ppm; coupling constants are given in Hz. IR spectra were obtained on potassium bromide pellets. Microanalyses were performed by MHW Laboratories, Phoenix, AZ. Compounds **2a** and **4**−**8** were obtained as previously described.[2]

***cis*-4,4a,9,9a-Tetrahydro-2-(1*H*-indol-3-yl)-4,4-dimethyl-3*H*-carbazole (2a):** yellow needles, mp 167−168 °C (lit. mp 170 °C,[2] 170−171 °C[1]); ^{1}H NMR (CDCl$_3$, 79.4 MHz) 0.94 (s), 1.19 (s, area for 0.94-1.19 is 6 H), 2.36 (s, 2 H), 3.10 (broad d, 1 H, J = 8), 4.52 (dd, 1 H, J = 8, 4), 6.25 (broad d, 1 H, J = 4), 6.72 (dt, 2 H, J = 9.2, 2.4), 6.94−7.44 (m, 7 H), 7.84−8.24 (m, 2 H); decoupling experiments: irradiation at 3.10 caused the dd at 4.52 to become a d and the broad d at 6.25 to become a clean d, irradiation at 4.52 caused the broad d's at 3.10 and 6.25 to become s's, irradiation at 6.25 caused the broad d at 3.10 and the dd at 4.52 to become clean d's; MS m/z (relative intensity) 314 (M$^{\bullet+}$, 37), 312 (12), 300 (22), 299 (100), 284 (23), 149.5 (23), 142 (14), 128 (11).

1,1′,4,4′-Tetrahydro-1,1,1′,1′-tetramethyl-3,3′(2*H*,2′*H*)-spirobi[cyclopent[*b*]indole] (4): mp of our colorless crystals used for mixture 249−251 °C; mp of sample supplied by Banerji *et al.*[6] 243−245 °C; mp of mixture 243−247 °C.

1,3′,4,4′-Tetrahydro-1,1,4′,4′-tetramethyl-*cis*-dispiro[cyclopent[*b*]indole-3(2*H*),2′(5′*H*)-furan-5′,3″-[3*H*]-indol]-2″-(1″*H*)-one (5): mp 262−263 °C; mp of our white crystals used for mixture 259−260 °C; mp of sample supplied by Banerji *et al.*[6] 247−250 °C; mp of mixture 251−252 °C.

1,4-Dihydro-1,1,5′,5′-tetramethylspiro[cyclopent[*b*]indole-3(2*H*), 3′(4′*H*)-1-benzazocine]-2′(1′*H*),6′(5′*H*)-dione (6): white crystals, mp 157−162 °C; ^{1}H NMR (CDCl$_3$, 79.4 MHz) 1.20 (s), 1.31 (s), 1.41 (s), 1.49 (s, area for 1.20−1.49 is 12 H), 1.88 (d, 1 H, J = 13), 2.06 (d, J = 16.5), 2.26 (d, J = 16.5, area for 2.06−2.26 is 2 H), 2.94 (d, 1 H, J = 13), 6.92−7.66 (m, 9 H), 7.89 (broad s, 1 H); ^{13}C NMR (pyridine-d_5, 25.2 MHz) 23.0, 28.9, 29.9, 30.3, 38.7, 49.5, 53.1, 55.5, 62.9, 112.9, 118.6, 119.3, 121.1, 123.6, 125.7 (2), 127.9, 128.1, 130.5, 134.1, 141.0, 142.9, 146.0, 175.8, 213.5; UV (95% EtOH) $\lambda_{\max}$ (log ϵ) 226 nm (4.68), 275 (3.95), 280 (sh, 3.95), 290 (sh, 3.85); IR 3380, 3160, 1700, 1655 cm^{-1}; HR MS m/z (relative intensity, calcd) 387.2009 (13, $^{12}C_{24}{}^{13}CH_{26}N_2O_2$, 387.2028), 386.2017 (59, $C_{25}H_{26}N_2O_2$, 386.1995).

4,4a-Dihydro-2-(3-1*H*-indolyl)-4,4-dimethyl-3*H*-carbazol-4a-ol (7): bright yellow flakes (EtOH), mp 229−231 °C (lit.[2] mp 230−231 °C); ^{1}H NMR (DMSO-d_6, 300 MHz) 0.53 (s, 3 H), 1.44 (s, 3 H), 2.54 (d, 1 H, J = 17.3), 3.08 (d, 1 H, J = 17.3), 5.69 (s, 1 H), 6.93 (d, 1 H, J = 1.8), 7.10−7.49 (m, 7 H), 7.70 (s, 1 H), 7.93 (d, 1 H, J = 8.6), 11.68 (s, 1 H); MS m/z (relative intensity) 329 (M$^{\bullet+}$ + 1, 21), 328 (M$^{\bullet+}$, 100), 313 (32), 312 (21), 310 (49), 299 (24), 297 (35), 285 (29), 282 (30).

5-(2-Aminophenyl)-1,3,4,5-tetrahydro-1,1,4,4-tetramethylcyclopent[*kl*]acridine (8): clear and tan crystals, mp 248−251 °C (lit.[2] mp 260 °C); ^{1}H NMR (DMSO-d_6, 300 MHz) 0.96 (s), 0.99 (s, area for 0.96−0.99 is 6 H), 1.52 (s, 3 H), 1.60 (s, 3 H), 2.30 (d, 1 H, J = 16.4), 2.60 (d, 1 H, J = 16.6), 4.33 (s, 1 H), 5.31 (s, 2 H), 6.17 (d, 1 H, J = 7.5) 6.25 (t, 1 H, J = 7.4), 6.33 (s, 1 H), 6.68 (d, 1 H, J = 7.8), 6.82 (t, 1 H, J = 7.1), 7.60 (m, 2 H), 7.95 (d, 1 H, J = 7.9), 8.12 (d, 1 H, J = 6.7); ^{13}C NMR (DMSO-d_6, 50 MHz) 23.4, 23.7, 26.2, 28.3, 33.9, 37.6, 48.4, 52.5, 115.3, 115.7, 123.6, 123.7, 125.6, 125.8, 126.5, 127.5, 129.1, 130.0, 133.3, 134.3, 141.9, 147.3, 147.7, 153.5, 158.1; MS m/z (relative intensity) 354 (M$^{\bullet+}$ + 1, 11), 353 (M$^{\bullet+}$, 38), 340 (26), 339 (100), 309 (22).

X-ray Structure of 8. 5-(2-Aminophenyl)-1,3,4,5-tetrahydro-1,1,4,4-tetramethylcyclopent[*kl*]acridine, $C_{25}H_{26}N_2$: M_r = 354.49, monoclinic, space group $P2_1/n$, a = 10.883(2) Å, b = 16.728(2) Å, c = 11.781(0) Å, β = 113.503(4)°, V = 1966.8(5) Å^3, Z = 4, D_x = 1.197 g cm^{-3}, λ(Cu Kα) = 1.5418 Å, linear absorption coefficient μ = 6.3 cm^{-1}, and F(000) = 760. The data were collected at a temperature of 298 K on an Enraf-Nonius CAD4 diffractometer: colorless needles, 0.16 × 0.15 × 0.35 mm; density not measured; 25 reflections with $20 \le \theta \le 25°$, Cu Kα_1 used to refine cell dimensions; systematic absences. $k = 0$, $h + l \neq 2n$; $0k0$, $k \neq 2n$ determined space group; no absorption correction was applied; $2\theta_{\max} = 120°$; $-12 \le h \le 11$, $0 \le k \le 18$, $0 \le l \le 13$; three standard reflections measured after every 3600 s of X-ray exposure indicated less than 1% decay; 3081 total reflections, 2911 unique, $R_i = 0.02$, 2402 observed [$I \ge 2.0\sigma(I)$]; structure was solved by direct methods; refinement on F, function minimized during refinement was $\Sigma w(F_o - F_c)^2$, with $w = 1/[\sigma^2(F) + 0.0005(F^2)]$; H atoms were located in a difference map and refined with isotropic thermal parameters; non-H atoms were refined with anisotropic thermal parameters: $R = 0.037$, $R_w = 0.051$, $S = 1.64$; $(\Delta/\sigma)_{\max} = 0.2\%$, final difference map maximum = 0.10 e Å^3, minimum = −0.18 e Å^3. Atomic scattering factors and anomalous dispersion corrections are from ref 10; structure solution and all calculations were performed with the NRCVAX[11] program suite.

Tables of atomic coordinates, anisotropic thermal parameters, bond distances and angles, and structure factors are available upon request.[12]

Acknowledgment. We thank Mrs. A. Chatterjee for supplying us with samples of compounds **3** and **4** for our mixture melting points and Professor J. Bergman for valuable discussions. M.J.K. thanks the Wayland E. Noland Research Fellowship Fund for financial support and L.M.C.K. thanks the National Science Foundation for an NSF-REU 1988 Summer Fellowship (Grant NSF/CHE 8712736-01).

JO951596P

---

(10) *International Tables for X-ray Crystallography*; Kynoch Press: Birmingham U.K. (present distributor D. Reidel: Dordrecht, Neth.), 1974; Vol. IV.

(11) Gabe, E. J.; Le Page, Y.; Charland, J.-P.; White, P. S. *J. Appl. Crystallogr.* **1989**, *22*, 384−387.

(12) The authors have deposited the atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, upon request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.