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Photooxygenation of 1,2,3,4-Tetrahydrocarbazole: Synthesis of Spiro[cyclopentane-1,2′-indolin-3′-one]

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Introduction

The reaction of singlet oxygen with 9-methyl-1,2,3,4-tetrahydrocarbazole has been observed to give a benzazonine derivative in good yield.[1] However, in common practice, the photooxygenation of olefins with singlet oxygen provides a convenient and effective route to allylic hydroperoxides.[2]

Spiro compound **3** was prepared in 1951 by Witkop[3] and co-workers, who were studying the mechanism of oxidation of 1,2,3,4-tetrahydrocarbazole with platinum catalyst. Recently, we have isolated **3** from the reaction of 1,2,3,4-tetrahydrocarbazolylmagnesium iodide with oxygen in good yield,[4] although the crude reaction product was resistant to complete purification.

We desired a good preparation of the spiro derivative **3**, which would be used as a starting material for the synthesis of spiro analogues of the ergot alkaloids.[5]

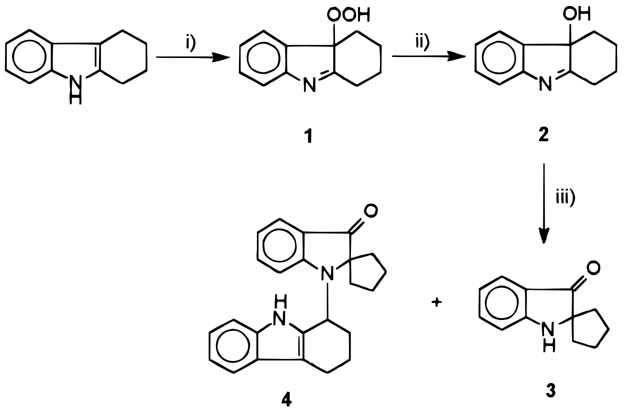
Results and Discussion

The synthesis of spiro derivative **3** was undertaken by employing a photooxygenation of 1,2,3,4-tetrahydrocarbazole using rose bengal supported on a strongly basic anion exchange resin as a photosensitizer (Scheme 1). From the first stage of the oxygenation was recovered a white solid, which proved to be an excellent yield of 4a-hydroperoxy-1,2,3,4-tetrahydro-4a*H*-carbazole (**1**): IR, 3100−2900 cm^{-1}; ^{1}H-NMR, 9.95 ppm (OO*H*); ^{13}C-NMR, 121.5 ppm (*C*-OOH); MS, M$^+$, 203 (15%).

4a-Hydroperoxy derivative **1** was converted to the 4a-hydroxy derivative **2** (89%), which partially rearranged to spiro derivative **3** (11%) upon reduction with an aqueous solution of sodium sulfite (10%) in methanol at room temperature.

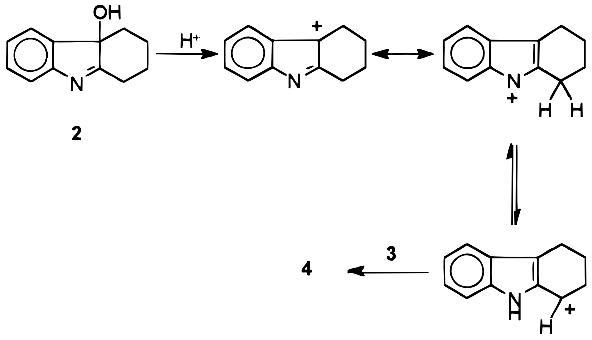
However, hydrogenolysis of the hydroperoxy group of **1** to produce the 4a-hydroxy derivative **2** was also attempted in the absence of a catalyst at atmospheric pressure, resulting in the 4a-hydroxy derivative **2** in 75% yield. In the presence of Pd/(C) in methanol (or PtO_2 in ethyl acetate), **1** gave 1,2,3,4-tetrahydrocarbazole in practically quantitative yield. 4a-Hydroxy and 4a-hydroperoxy derivatives exhibit similar spectra.

Scheme 1



i) $^1O_2$, polymer supported rose bengal; ii) Na_2SO_3/H_2O (10%); iii) H_2SO_4/H_2O (10%).

Scheme 2



The 4a-hydroxy derivative **2** completely rearranged to the spiro derivative **3** in 98% yield upon treatment with a mineral acid catalyst. Subsequently, spiro derivative **3** transforms to condensed product **4** in moderate yield if the reaction time exceeds 5 h.

Formation of compound **4** can be rationalized by a nucleophilic attack of spiro compound **3** on a carbocation intermediate, as shown in Scheme 2.

Compounds **3** and **4** in solution show solvent dependent fluorescence radiation with significant quantic yields.[6]

The IR spectrum of the condensed spiro compound **4** has absorption bands at 1670 and 3260 cm^{-1}, which indicate the presence of C=O and NH groups, respectively. The ^{1}H-NMR spectrum shows a broad singlet at 8.40 ppm that confirms the presence of a NH bond, while the ^{13}C-NMR spectrum reveals a carbonyl group at 218.1 ppm. The mass spectrum displays a mass ion of 356. Spiro compound **4** was thus assigned the structure shown, which was confirmed by single-crystal X-ray analysis.

Molecular Structure of 4. The structure of compound **4** is shown in the Figure 1 together with its numbering scheme.

The atomic distances in the indoline group are very similar to those found in Uvarindole D,[7] in which there may exist a conjugation through most of the indoline ring, with N1−C2 and C7−C8 bond distances shorter than those expected for a single bond and alternated short and long distances in the benzene ring of the indoline nucleus.

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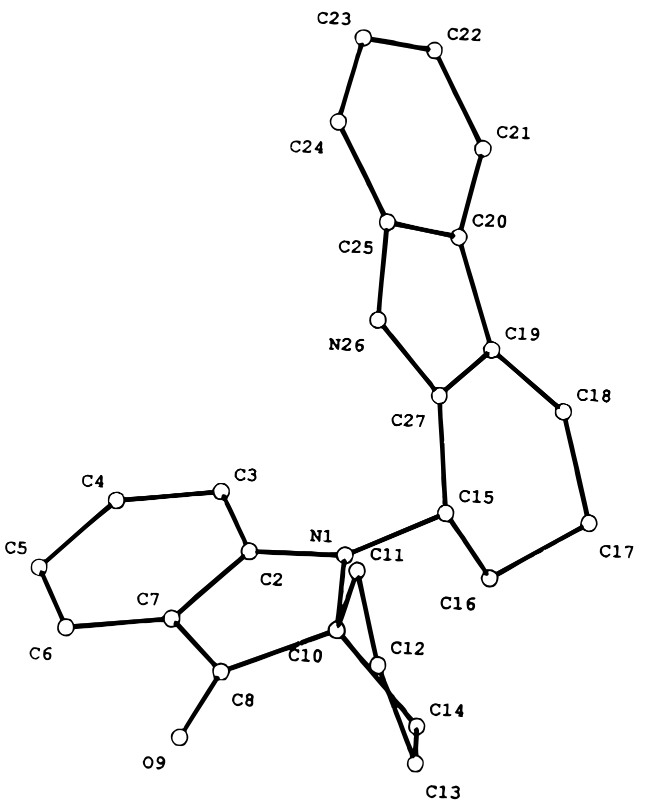

Figure 1. View of the molecule showing the atomic numbering.

Moreover, the shortening of the C7−C8 bond can be attributed to the conjugation of the phenyl ring with the carbonyl group and to steric crowding at C10, such that the C8−C10 bond stretches to 1.529(2) Å to accommodate the large C10 substituent.

The indoline ring of the molecule is planar, the angle between the indoline nucleus and its benzene ring being only 0.68(6)°. The spiro cyclopentane ring has an envelope conformation with C10 0.596 Å out of the plane formed by the other four atoms and the torsional angle between C11−C12−C13−C14 and C11−C10−C14 being 37.8°. The cyclohexa[*b*]indole system is less planar than the indoline system, the angles formed between the indole nucleus and its benzene ring and the cyclohexene ring being 1.34(6)° and 2.49(8)°, respectively, while C16 is 0.449 Å above and C17 is −0.304 Å below the plane formed by C15−C27−C19−C18. The cyclohexene ring has a half-chair conformation.[8] The angle formed by the two moieties of the molecule is 70.88(4)°, the torsion angle around N1−C15 being −67.8(2)°. The N1 atom of the indole group is linked to C15 of the cyclohexene ring.

The packing of the molecules is governed by two factors: (i) the molecules are linked in pairs by a contact between the ring systems that gives a distance of 4.07 Å between the centroid of the five-membered ring and the centroid of the cyclohexene;[9] (ii) there is a hydrogen bond, N26···O9 2.886(2) Å, N26−H26···O9 164(2)° ($^1/_2 - x$, $^1/_2 + y$, $2 - z$), that links the molecules in zigzag fashion, forming chains along the *b* axis.

Experimental Section

General Methods. Melting points were determined in open capillary tubes and are uncorrected. Nuclear magnetic resonance spectra were recorded at 200 MHz. Mass spectra were recorded using an electronic impact technique. All solvents and chemicals were reagent grade.

4a-Hydroperoxy-1,2,3,4-tetrahydro-4a*H*-carbazole (1). A mixture of 1,2,3,4-tetrahydrocarbazole (1.0 g, 5.8 mmol) in 10 mL of dry toluene and 1.0 g of rose bengal supported on a strongly basic anion exchange resin (Lewatit M-500) was stirred in an oxygen atmosphere and was irradiated with sunlight for 24 h. The 4a-hydroperoxy-1,2,3,4-tetrahydro-4a*H*-carbazole was filtered together with the resin and extracted with dichloromethane. After evaporation of the solvent, the hydroperoxy derivative was isolated as a yellow solid, which was recrystallized from toluene−petroleum ether (1:1) to separate colorless crystals, mp 127−129 °C dec, 1.07 g, in 90% yield.

IR (KBr): 3100−2900 cm^{-1}. ^{1}H-NMR (CDCl$_3$): δ 9.95 (s, 1H). ^{13}C-NMR (CDCl$_3$): δ 121.5. MS (70 eV): *m/z* 203 (M$^+$, 15). The rest of the data of the spectrum are analogous to those of the 4a-hydroxy-1,2,3,4-tetrahydro-4a*H*-carbazole. Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.63; H, 6.70; N, 7.12.

4a-Hydroxy-1,2,3,4-tetrahydrocarbazole (2). A solution of 4a-hydroperoxy-1,2,3,4-tetrahydro-4a*H*-carbazole (1.07 g, 5.3 mmol) in 40 mL of methanol was stirred with 30 mL of an aqueous solution of sodium sulfite (10%) at room temperature for 15 h. The mixture was extracted with dichloromethane, and after evaporation of the solvent, 4a-hydroxy-1,2,3,4-tetrahydro-4a*H*-carbazole was isolated as a yellow solid, which was recrystallized from toluene−petroleum ether (1:1) to obtain colorless crystals, mp 158−159 °C dec, 0.88 g, in 89% yield. Spiro derivative **3** appears in 11% yield.

IR (KBr): 3300−3000, 1600, 1100, 770 cm^{-1}. ^{1}H-NMR (CDCl$_3$): δ 7.45−7.15 (m, 4H), 2.70 (m, 1H), 2.65 (s, 1H), 2.55 (dt, 1H, $J_1 = 3.0$ Hz, $J_2 = 14.0$ Hz), 2.15 (m, 1H), 1.95 (tt, 1H, $J_1 = 3.6$ Hz, $J_2 = 13.5$ Hz), 1.65 (m, 2H), 1.40 (m, 1H), 1.23 (dt, 1H, $J_1 = 4.0$ Hz, $J_2 = 13.7$ Hz). ^{13}C-NMR (CDCl$_3$): δ 188.7, 152.0, 42.3, 128.7, 125.3, 122.1, 119.7, 81.1, 39.0, 28.7, 28.32, 20.4. MS (70 eV): *m/z* 187 (M$^+$, 100), 168 (38), 159 (35), 146 (65), 130 (35), 117 (22), 105 (13), 89 (14), 77 (32). Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.65; H, 7.15; N, 7.33.

Spiro[cyclopentane-1,2′-indolin-3′-one] (3). A solution of 4a-hydroxy-1,2,3,4-tetrahydro-4a*H*-carbazole (0.37 g, 2.0 mmol) in 30 mL of absolute methanol was treated with 10 mL of an aqueous solution of sulfuric acid (10%) at room temperature. After 20 min the mixture was extracted with petroleum ether, and the solvent was removed under reduced pressure to separate a yellow solid, mp 78−79 °C, 0.36 g, 98% yield, which was identificated as spiro[cyclopentane-1,2′-indolin-3′-one].[3,4]

IR (Nujol): 3290, 1670, 1490−1460, 750 cm^{-1}. ^{1}H-NMR (CDCl$_3$): δ 7.50 (m, 2H), 6.80 (m, 2H), 4.90 (s, 1H), 1.90 (m, 8H). ^{13}C-NMR (CDCl$_3$): δ 205.2, 160.0, 136.8, 124.5, 120.6, 118.6, 112.2, 74.4, 38.0, 25.4. MS (70 eV): *m/z* 187 (M$^+$, 28), 159 (29), 158 (100), 130 (41), 77 (49).

Compound **4** was isolated when the time of the above reaction exceeded 5 h. Then, the mixture was extracted with dichloromethane and after solvent evaporation under reduced pressure yielded a brown solid, which was recrystallized from hexane to obtain yellow crystals, mp 206−208 °C, 0.12 g, 35% yield, which were identified as **4**.

IR (KBr): 3260, 1670, 745 cm^{-1}. ^{1}H-NMR (CDCl$_3$): δ 8.40 (s, 1H), 7.55 (d, 1H, $J = 6.5$ Hz), 7.15 (m, 4H), 7.10 (m, 1H), 6.60 (t, 1H, $J = 7.4$ Hz), 6.10 (d, 1H, $J = 8.5$ Hz), 4.85 (m, 1H), 2.90 (m, 2H), 2.50−1.80 (m, 12H). ^{13}C-NMR (CDCl$_3$): δ 218.1, 157.7, 137.0, 136.0, 127.5, 124.6, 124.0, 121.8, 119.3, 119.0, 118.3, 116.8, 112.1, 111.1, 110.8, 76.8, 49.8, 35.1, 34.9, 28.0, 25.9, 25.8, 23.4, 20.6. MS (70 eV): *m/z* 356 (M$^+$, 2), 187 (38), 169 (71), 168 (100), 158 (68). Anal. Calcd for $C_{24}H_{24}N_2O$: C, 80.87; H, 6.79; N, 7.86. Found: C, 80.65; H, 6.85; N, 7.59.

X-ray Crystallographic Analysis of 4. Yellow crystals of **4** for X-ray analysis were obtained from slow evaporation of a dilute toluene solution. A crystal 0.38 × 0.32 × 0.21 mm was used for the crystallography study. Accurate cell dimensions were determined by least-squares analysis of setting angles of 60 reflections ($4 < \theta < 35°$), using graphite-monochromated Cu Kα radiation ($\lambda = 1.5418$ Å) automatically located and centered on a four-circle diffractometer. The crystals are monoclinic, space group $P2_1/a$, with $a = 20.581(1)$ Å, $b = 9.804(1)$ Å, $c = 9.270(1)$ Å, $\beta = 95.480(4)°$, and $V = 1861.9(3)$ Å^3. The molecular

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formula is $C_{24}H_{24}N_2O$, molecular weight is 356.466, $D_c = 1.272(3)$ g·cm^{-3}, $Z = 4$, and $F(000) = 760$. Correction by μ absorption was neglected; $\mu = 5.715(5)$ cm^{-1}.[14]

Two reflections were measured every 90 min to ascertain crystal stability, and no significant variation was observed. All the reflections were corrected for Lorentz and polarization effects, but no absorption correction was applied. For the intensity measurement, reflections were surveyed in the range $2 < 2\theta < 65°$; from 3170 independent reflections measured, 2645 were considered as observed, satisfying the criterion $I > 2\sigma(I)$ in the range $h \pm 25$, k 0/12, l 0/11, and were used in the subsequent calculations.[10]

The crystal structure was partially elucidated by direct methods.[11] After preliminary adjustment of the weight atoms, H-atoms were positioned from difference Fourier maps. Thereafter, several cycles of full-matrix least-squares calculations were carried out with anisotropic thermal parameters for weight atoms; the H-atoms were included as fixed contributors, and convergence was reached at $R = 0.044$ and $R_w = 0.051$ with a weighting scheme[12] to prevent trends in $w\Delta^2F$ vs $\langle F_o \rangle$ and vs $\langle \sin \theta/\lambda \rangle$. The final difference synthesis showed no peaks exceeding 0.30 e Å^3.

The atomic scattering factors and the anomalous dispersion correction were taken from the literature.[13]

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[14] The author has deposited atomic coordinates for the structure of **4** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.