First Transformations of Pyrano[3,4-*b*]indol-3-ones to Salvadoricine and 2,3-Diacylindoles

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The readily available methylated pyrano[3,4-*b*]indol-3-ones **1a** and **1b** were hydrolyzed to furnish the 2-acetylindol-3-alkanoic acids **2** and **4**. Compound **2** was easily transformed selectively to 2-acetyl-3-methylindole (**3**, salvadoricine). Substrate **1b** reacts with molecular oxygen from the air only in the presence of a catalyst to give 2,3-diacetylindole (**5**) while **1a** reacts with nitrosobenzene *via* a proposed Diels-Alder step to yield 2-acetylindole-3-carbaldehyde (**6**). The latter product can also be obtained in low yield from the reaction of **1a** with molecular oxygen from the air.

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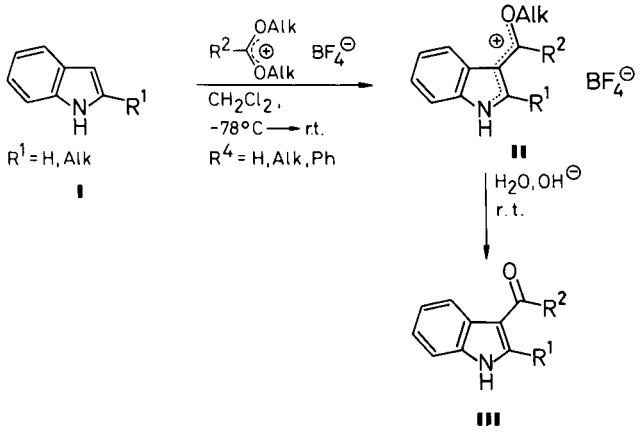
The syntheses of acylindoles - interesting building blocks in alkaloid chemistry - have been widely documented and numerous efficient strategies have been developed in the past 30 years [1-4]. One of the more recent methods for the acylation of indoles is the highly efficient, high-yielding, and mild reaction of indoles **I** with dialkoxycarbenium tetrafluoroborates which yields the 3-acylindoles **III** as outlined in Scheme 1.

Scheme 1



In contrast, the regioselective synthesis of 2-acylated indoles is more difficult [1-4]. Products of this type are usually obtained by way of processes involving special indolization strategies [8] or using *N*-protected 2-metallated indoles as intermediates [9]. In the present paper, we report on the continuation of our investigations of the reactivity of pyrano[3,4-*b*]indol-3-ones **1a** and **1b** [10,11] to include their transformations to acylindoles.

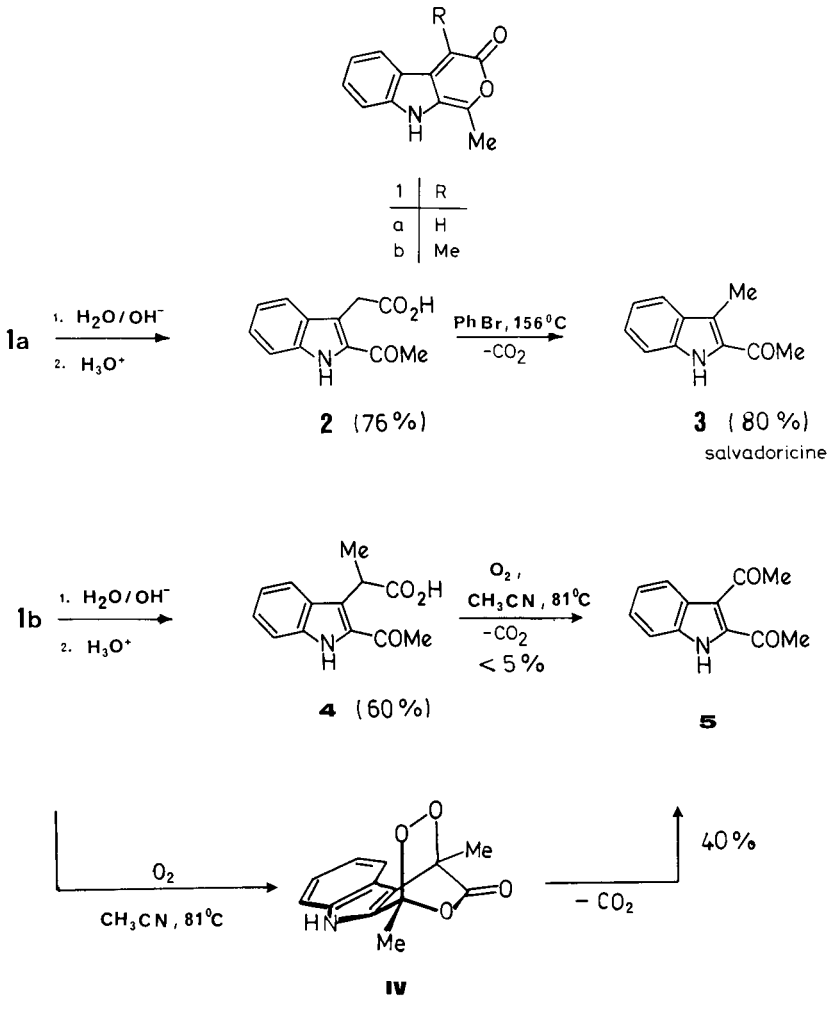
The readily available 1-methylpyrano[3,4-*b*]indol-3-one (**1a**) [11] underwent alkaline hydrolysis to furnish the 2-acylindol-3-acetic acid (**2**) in 76% yield which, in turn, underwent decarboxylation on refluxing in bromobenzene to give 2-acetyl-3-methylindole (**3**) (Scheme 2). Similarly, **1b** was hydrolyzed to the 2-acetylindole-3-propanoic acid **4** in 60% yield (Scheme 2). However, the oxidative decarboxylation of **4** to **5** did not occur under an inert gas atmosphere although product **4** did react to a small extent with atmospheric oxygen to furnish **5** (<5%, by pmr and tlc). On the other hand, **1b** in absolute solvents reacted with atmospheric oxygen to furnish 2,3-diacetylindole (**5**) exclusively. We propose the following mechanism for this direct transformation of **1b** to **5**: a [4 + 2] cycloaddition of **1b** with oxygen gives the bridged intermediate **IV** which is subsequently stabilized by extrusion of carbon dioxide and cleavage of the peroxo bond. A related mechanism has been postulated previously [12].

In analogy to the reaction of atmospheric oxygen with **1b**, we have attempted to convert the monomethyl derivative **1a** to the expected 2-acetylindole-3-carbaldehyde (**6**) by reaction with atmospheric oxygen under absolute conditions. However, after refluxing of **1a** in bromobenzene for 4 days, product **6** was obtained merely in 10% yield. For this reaction as well, we suggest an analogous mechanism involving a cycloadduct structurally related to **IV** (Scheme 2).

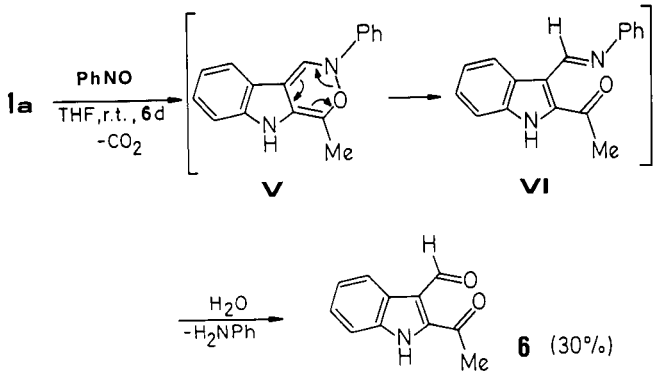
In the light of our extensive investigations on Diels-Alder reactions of **1a** and **1b** with carbodienophiles to produce carbazole derivatives [10], we have now looked at the reactions of **1a** and **1b** with some common heterodienophiles. The reaction of **1a** with the dienophilic nitrosobenzene (Scheme 3) provided an interesting result for which we suggest the following mechanism [10]: Diels-Alder reaction to give the intermediate **V** which is stabilized by ring cleavage at the labile N-O bond to furnish **VI**. This highly sensitive aldimine system should then undergo hydrolysis to the more stable product **6**. Although the regiochemistry of the Diels-Alder step in Scheme 3 could be reversed, the subsequent cleavage product of the alternative primary intermediate should lead to the same product **6**.

2-Acetyl-3-methylindole (**3**) is the alkaloid salvadoricine that was first isolated from the leaves of *Salvadora persica* [13a] which are used in folk medicine as an odontological

Scheme 2



Scheme 3



remedy. The constitutions of the indole derivatives **2-6** were elucidated unambiguously with the help of ^{1}H,^{1}H-nOe experiments above all.

In summary, the present results illustrate simple approaches to acylindoles from the readily available pyranoindolones **1a** and **1b** as well as a novel, high-yielding route to the alkaloid salvadoricine [13b]. In these reactions, oxygen and nitrosobenzene act as "dienophilic" reagents to catalyse the formation of 2,3-diacylindoles. In contrast, the alternative syntheses of **2** and **4**, such as the acetylation of the corresponding indol-3-alkanoic acids for example, are more difficult. In this context, it should be mentioned that indol-3-acetic acid has been transformed to **2**, albeit in low yield, by the action of acetic anhydride/boron trifluoride etherate [14]. Hence, the present results demonstrate that compounds **1a** and **1b** represent synthetic equivalents of **2** and **4**.

EXPERIMENTAL

Materials and Techniques.

Melting points were determined on a Büchi SMP 20 apparatus and are not corrected. The ^{1}H- and ^{13}C-nmr spectra were recorded on a Bruker WM-400 spectrometer at 400 and 100.6 MHz, respectively, using tetramethylsilane as an internal standard. The ei mass spectra (70 eV) were measured on a Varian MAT 7 spectrometer. Merck silica gel 60 (grain size: 0.040-0.063 mm) was

used for "flash" chromatography. Centrifugal layer chromatography was performed with a Harrison Research Chromatotron Type 7924T apparatus on Merck silica gel 60 F_{254}. Elemental analyses were performed using a Carlo Erba Strumentazione apparatus.

1-(3-Methyl-1*H*-indol-2-yl)ethanone (**3**).

2-Acetylindol-3-acetic acid (**2**) (217 mg, 1 mmole) in 20 ml of bromobenzene was heated under reflux at 156° for 3-4 days. The organic solvent was removed and the residue (about 2 ml) was purified by centrifugal layer chromatography (eluent: 40-60° petroleum ether/ethyl acetate, 3/1) to furnish product **3** in 80% yield (138 mg), mp 145-146° (petroleum ether/ethyl acetate), ref [14b], mp 143-144°; ^{1}H-nmr (hexadeuteriodimethyl sulfoxide): δ 2.56 (s, 6H, C3-CH_3 and $COCH_3$), 7.05 (dd, ^{3}J = 7.35 Hz, ^{3}J = 7.53 Hz, 1H, C5-H), 7.26 (dd, ^{3}J = 7.89 Hz, ^{3}J = 7.35 Hz, 1H, C6-H), 7.39 (d, ^{3}J = 8.25 Hz, 1H, C7-H), 7.68 (d, ^{3}J = 8.05 Hz, 1H, C4-H), 11.41 (s, 1H, NH); ^{13}C-nmr (hexadeuteriodimethyl sulfoxide): δ 10.41 (C2-CH_3), 28.84 ($CO\mathit{C}H_3$), 112.33, 117.55, 119.31, 120.69, 125.34, 127.92, 132.03 (Cq), 136.05, 190.51 (CO); ei-ms: m/e (%) 173 ($M^{+\cdot}$, 100), 158 ($M^{+\cdot}$-CH_3, 99), 130 ($M^{+\cdot}$-$COCH_3$, 95), 103 (65), 77 (73).

Anal. Calcd. for $C_{11}H_{11}NO$ (173.21): C, 76.28; H, 6.40; N, 8.09. Found: C, 75.99; H, 6.60; N, 8.29.

2-Acetylindol-3-acetic Acid (**2**).

The pyranoindolone **1a** (199 mg, 1 mmole) was suspended in a mixture of 10 ml of 10% aqueous sodium hydroxide solution and 5 ml of 96% ethanol. The mixture was heated under reflux for 0.5 hour, cooled, and the free acid **2** precipitated by addition of 5% hydrochloric acid. The product was recrystallized from 96% ethanol in 76% yield (166 mg), mp 216°, ref [11], mp 214°; ^{1}H-nmr (hexadeuteriodimethyl sulfoxide): δ 2.55 (s, 3H, CH_3), 4.05 (s, 2H, CH_2), 7.05 (ddd, ^{3}J = 7.2 Hz, ^{3}J = 7.9 Hz, ^{4}J = 2 Hz, 1H, C5-H), 7.28 (ddd, ^{3}J = 7.8 Hz, ^{3}J = 7.4 Hz, ^{4}J = 2 Hz, 1H, C6-H), 7.43 (d, ^{3}J = 7.8 Hz, 1H, C7-H), 7.66 (d, ^{3}J = 8.1 Hz, 1H, C4-H), 11.63 (s, 1H, NH or OH), 12.25 (s, 1H, OH or NH); ei-ms: m/e (%) 217 ($M^{+\cdot}$, 52), 200 ($M^{+\cdot}$-OH, 21), 172 ($M^{+\cdot}$-CO_2H, 100).

Anal. Calcd. for $C_{12}H_{11}NO_3$ (217.23): C, 66.35; H, 5.10; N, 6.45. Found: C, 66.36; H, 5.15; N, 6.21.

2-(2-Acetyl-1*H*-indol-3-yl)propanoic Acid (**4**).

The pyranoindolone **1b** (213 mg, 1 mmole) was suspended in a mixture of 10 ml of 10% aqueous sodium hydroxide solution and 5 ml of 96% ethanol. The mixture was heated under reflux for 0.5 hour, cooled, and the free acid **4** precipitated by addition of 5% hydrochloric acid. The product was recrystallized from 96% ethanol in 60% yield (139 mg), mp 182-184°; ^{1}H-nmr (hexadeuteriodimethyl sulfoxide): δ 1.42 (d, ^{3}J = 7.16 Hz, 3H, CHCH_3), 2.59 (s, 3H, $COCH_3$), 4.76 (q, ^{3}J = 7.16 Hz, 1H, C$\mathit{H}$$CH_3$), 7.04 (ddd, ^{3}J = 7.06 Hz, ^{3}J = 8.14 Hz, ^{4}J = 0.72 Hz, 1H, C5-H), 7.27 (ddd, ^{3}J = 7.79 Hz, ^{3}J = 7.14 Hz, ^{4}J = 0.75 Hz, 1H, C6-H), 7.46 (d, ^{3}J = 8.33 Hz, 1H, C7-H), 7.64 (d, ^{3}J = 8.14 Hz, 1H, C4-H), 11.64 (s, 1H, NH or OH), 12.15 (s, 1H, OH or NH); ei-ms: m/e (%) 231 ($M^{+\cdot}$, 31), 213 ($M^{+\cdot}$-H_2O, 25), 186 ($M^{+\cdot}$-CO_2H, 100), 145 (91).

Anal. Calcd. for $C_{13}H_{13}NO_3$ (231.25): C, 67.52; H, 5.67; N, 6.06. Found: C, 67.20; H, 5.58; N, 5.78.

1-(2-Acetyl-1*H*-indol-3-yl)ethanone (**5**).

1,4-Dimethylpyrano[3,4-*b*]indol-3-one (**1b**) (213 mg, 1 mmole) was suspended in 20 ml of acetonitrile and heated at 81° for 4 days while passing air through the mixture. The organic solvent was removed and the residue (about 2 ml) was purified by centrifugal layer chromatography (petroleum ether/ethyl acetate, 3/1) to furnish the product **5** in 40% yield (40 mg), mp 123°, ref [12], mp 124°; ^{1}H-nmr (deuterioacetonitrile): δ 2.58 (s, 3H, $COCH_3$), 2.63 (s, 3H, $COCH_3$), 7.25 (dd, ^{3}J = 7.22 Hz, ^{3}J = 8.03 Hz, 1H, C5-H), 7.36 (dd, ^{3}J = 7.40 Hz, ^{3}J = 7.88 Hz, 1H, C6-H), 7.54 (d, ^{3}J = 8.38 Hz, 1H, C7-H), 7.90 (d, ^{3}J = 8.25 Hz, 1H, C4-H), 10.28 (s, 1H, NH); ei-ms: m/e (%) 201 ($M^{+\cdot}$, 70), 186 ($M^{+\cdot}$-CH_3, 100), 158 ($M^{+\cdot}$-$COCH_3$, 13), 144 (35), 116 (30).

Anal. Calcd. for $C_{12}H_{11}NO_2$ (201.22): C, 71.63; H, 5.51; N, 6.96. Found: C, 71.55; H, 5.67; N, 6.88.

2-Acetylindole-3-carbaldehyde (**6**) [15].

1-Methylpyrano[3,4-*b*]indol-3-one (**1a**) (200 mg, 1 mmole) and nitrosobenzene (160 mg, 1.5 mmoles) in 20 ml of tetrahydrofuran were stirred at 20° for 6 days under an inert gas atmosphere (nitrogen). The mixture was then concentrated under vacuum and the residue worked up by "flash" chromatography (40-60° petroleum ether/ethyl acetate, 6/4) to give the product **6** in 30% yield (60 mg), mp 176-179° (petroleum ether/ethyl acetate); ^{1}H-nmr (deuterioacetonitrile): δ 2.72 (s, 3H, CH_3), 7.32 (ddd, ^{3}J = 7.34 Hz, ^{3}J = 7.64 Hz, ^{4}J = 0.8 Hz, 1H, C5-H), 7.42 (ddd, ^{3}J = 8.26 Hz, ^{3}J = 7.10 Hz, ^{4}J = 1.10 Hz, 1H, C6-H), 7.58 (d, ^{3}J = 8.31 Hz, 1H, C7-H), 8.32 (d, ^{3}J = 8.09 Hz, 1H, C4-H), 10.55 (s, 1H, NH), 10.65 (s, 1H, CHO); ei-ms: m/e (%) 187 ($M^{+\cdot}$, 96), 159 ($M^{+\cdot}$-CO, 43), 144 ($M^{+\cdot}$-$COCH_3$, 100).

Anal. Calcd. for $C_{11}H_9NO_2$ (187.20): C, 70.58; H, 4.85; N, 7.48. Found: C, 70.40; H, 4.67; N, 7.35.

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