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Formation of yohimbanones via a novel rearrangement

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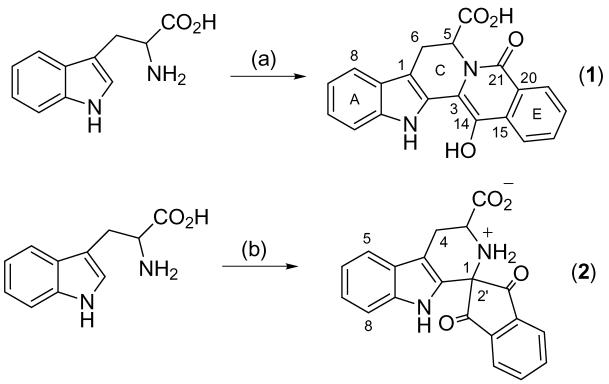
We are delighted to dedicate this paper to K. C. Nicolaou in recognition of his many contributions to organic chemistry and his receipt of the 2002 Tetrahedron Prize

Abstract—An investigation of the reaction of tryptophan and its methyl ester with ninhydrin has been conducted. In the reaction of tryptophan with ninhydrin only one product, yohimbanone (**1**), is isolated. In contrast, an intermediate, Pictet–Spengler product **3**, is isolated from the reaction of tryptophan methyl ester with ninhydrin. The isolation of this intermediate provides support for a proposed mechanism of this novel rearrangement, which is presented herein.

1. Introduction

The yohimbines, members of the Rauwolfia alkaloid family, have attracted a great deal of synthetic interest over the years[1,2] due to the interesting structures and diverse biological activities[3] of these alkaloids. For some time, it has been known that tryptophan and ninhydrin can be condensed to provide a pentacyclic indole alkaloid bearing a carbon skeleton reminiscent of yohimbane and reserpine. However, the details of this transformation, including the mechanism, have remained unclear. It was this uncertainty that led to our interest in this intriguing reaction.

In 1989, Neuzil and co-workers reported that the reaction of tryptophan with ninhydrin in aqueous acid at room temperature produced a yellow crystalline product, the structure of which was shown to be 5-carboxy-14-hydroxy-(3,14,15,16,17,18,19,20)-octadehydro-21-yohimbanone (**1**, Scheme 1) by X-ray diffractometry.[4] The structure of this product was determined after recrystallization from hot methanol. The yield of 20% could purportedly be improved by collecting the filtrate of the initial preparation and the methanol used for washing. While no NMR data was reported in this reference, the X-ray structure certainly defined the product and was used as the basis for 'eliminating' the previously proposed product,[5] a spiro-cyclic derivative of 1,2,3,4-tetrahydro-β-carboline (**2**). The same conditions had been reported by Heesing and co-workers to provide this zwitterionic product (**2**) twenty years earlier. This Pictet–Spengler product resembled products obtained by McLean,[6] Irie,[7] and Kametani[8] during their investigations of the reaction of 1,2-indanediones with tryptamine and derivatives.



Scheme 1. Conditions reported for the formation of **1**:[4] (a) ninhydrin, 0.1N HCl, 48 h (20%) and **2**:[5] (b) ninhydrin, 0.1N HCl, 48 h (39%).

This discrepancy proved interesting as did the potential mechanisms for formation of the fused pentacycle isolated by Neuzil and co-workers. Neuzil presented two main hypotheses for the formation of **1**. One relied upon the formation of *o*-carboxyphenylglyoxal from ninhydrin. This is a known reaction in a basic medium, but it is less probable in acidic medium, as Neuzil notes. The second postulated hypothesis suggests the intermediacy of a spiro β-carboline. Such compounds had been shown to rearrange to similar structures under UV irradiation.[7,8] However, no precedent existed for this type of rearrangement in aqueous acid.

2. Results and discussion

We were able to repeat the synthesis of **1**, obtaining an

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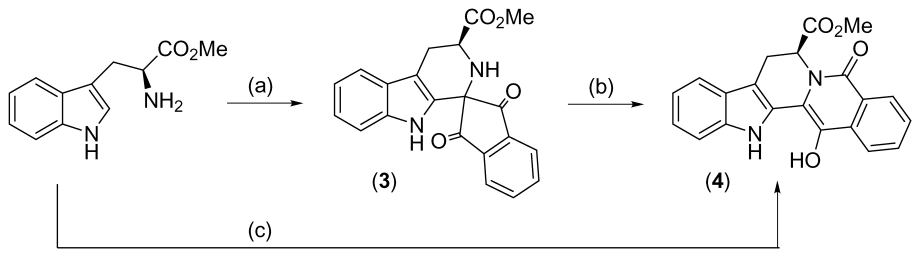


Scheme 2. (a) ninhydrin, 0.1N HCl, 48 h (56%); (b) $SnCl_2{\cdot}2H_2O$, MeOH, reflux, 22 h (46%); (c) ninhydrin, 0.1N HCl, reflux, 3 h (24%).

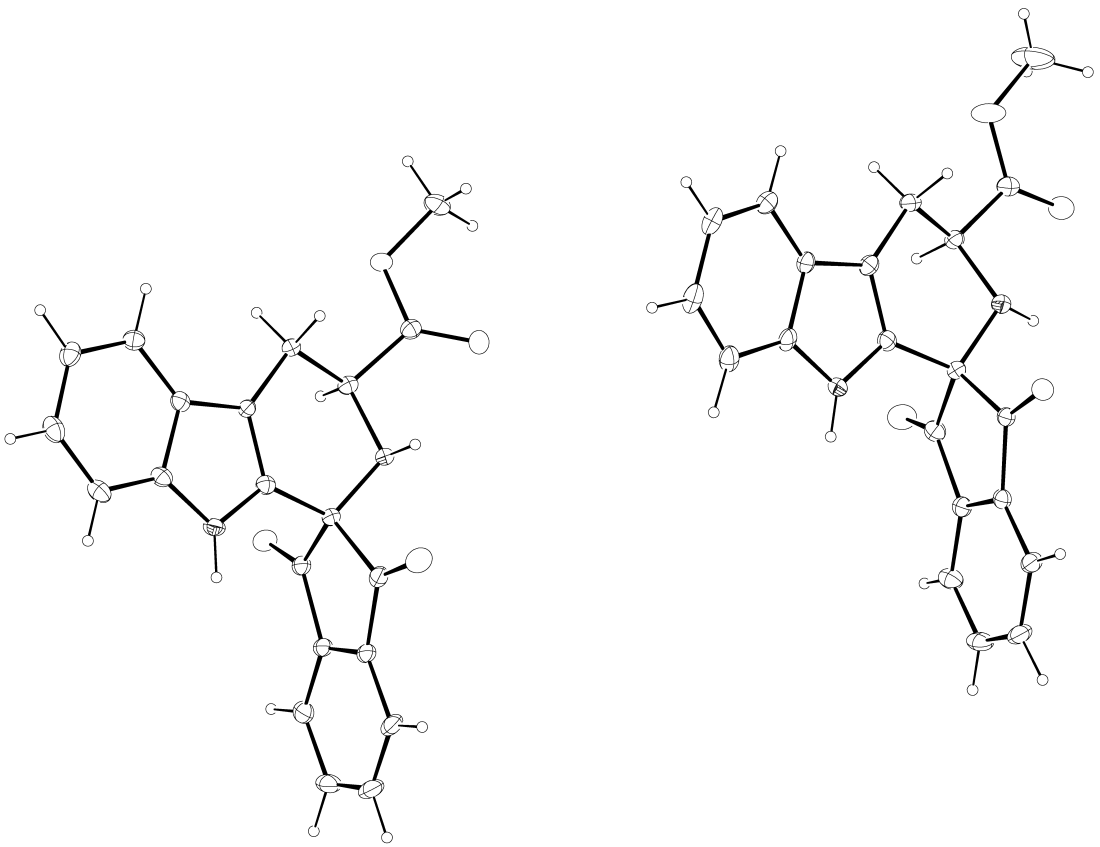


Figure 1. X-ray structures of the two conformations of **3** present in the unit cell.

X-ray structure of the product, as Neuzil had.[9] However, when L-tryptophan methyl ester was subjected to the same reaction conditions, the compound obtained corresponded to the Pictet–Spengler condensation product (**3**, Scheme 2). We speculated that, in the case of L-tryptophan, compound **2** is transiently formed but rearranges upon heating in methanol, during recrystallization, to yohimbanone **1**. Due to the carboxylic acid functionality, this recrystallization takes place in the presence of 1 equiv. of acid. In the case of the methyl ester, recrystallization occurs in a neutral environment. This allows for the isolation of **3** and accounts for the failure of **3** to spontaneously rearrange. Gratifyingly, it was discovered that heating compound **3** in a protic solvent with catalytic protic acid caused partial conversion to the fused yohimbanone **4**. We postulated that the rearrangement of **3** to **4** should be induced by Lewis acids as well as protic acid. After screening various conditions, it was found that heating **3** in methanol at reflux with stannous chloride dihydrate cleanly produced **4**, which was analytically pure after collection from the reaction mixture by filtration without any subsequent purification.

The structure of the Pictet–Spengler product **3** was confirmed by X-ray crystallography. Interestingly, two conformations of **3** were present in the asymmetric unit (Figure 1).

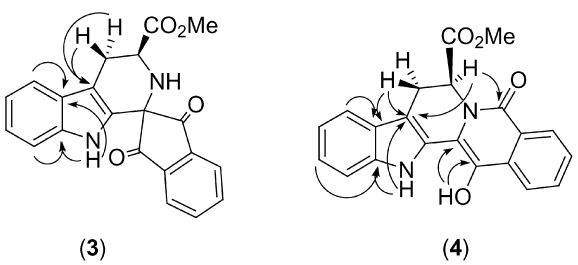
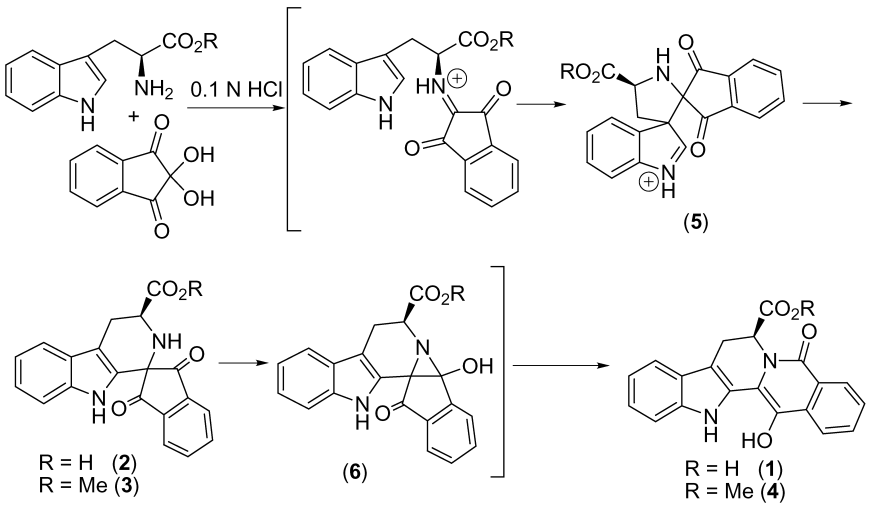


Figure 2. Selected HMBC correlations for **3** and **4**.



Scheme 3. Proposed mechanism for the formation of **1** and **4**.

The structure of rearrangement product **4** was supported by COSY, HMQC, and HMBC (Figure 2) correlation data as well as by comparison to the analytical data for yohimbanone **1**. Assignment of the spectral data of **1** was facilitated by the X-ray structure. A twist in the C ring of **1** puts H-6α in much closer proximity to H-8 than H-6β. As a result, a 5.7% NOE enhancement of H-8 was observed upon irradiation of H-6α.[9]

Based on the isolation of Pictet–Spengler product **3**, which has now been shown to be an intermediate in the conversion of tryptophan methyl ester to yohimbanone **4**, and on the observation that acidic conditions induce the rearrangement of **3** to **4**, we propose the mechanism shown in Scheme 3 for this novel rearrangement. Initial Pictet–Spengler reaction, proceeding through the typical spiroindolenine intermediate (**5**),[10] is followed by attack of the β-carboline nitrogen on the adjacent carbonyl of the indanedione moiety. Fragmentation of the resulting hydroxyaziridine (**6**) provides the yohimbanone skeleton (**1**, **4**). This mechanism is in accord with the known reactivity of ninhydrin and has the advantage of not invoking *o*-carboxyphenylglyoxal as an intermediate.

This novel rearrangement allows rapid entry to the yohimbane skeleton and is complementary to other approaches that provide different substitution patterns. Noteworthy among these is the sequential photochemical cyclization, acidic rearrangement of phthalimide Mannich bases devised by Coyle and co-workers[11–14] that provides the yohimbane skeleton[15] in four steps from phthalimide, tryptamine, and glyoxylic acid. This route provides a related yohimbanone without the 5-carboxy group.

The process described herein, originally observed by Neuzil and co-workers, provides yohimbanones directly from simple precursors and may find utility in analogue preparation. Our investigation of the reaction pathway, resulting in the isolation of intermediate **3** and its subsequent conversion to the yohimbane skeleton, suggests that the mechanism proceeds through Pictet–Spengler reaction followed by acid-mediated rearrangement, which should be applicable to the synthesis of related heterocyclic systems.

3. Experimental

3.1. General

Solvents were HPLC grade (methanol) or reagent grade (methylene chloride). Melting points (°C) were determined using a Thomas–Hoover melting point apparatus and are uncorrected. Proton magnetic resonance spectra (^{1}H NMR) and carbon magnetic resonance spectra (^{13}C NMR) were recorded on a Bruker AMX-500 spectrometer operating at 500 MHz. Infrared spectra (IR) were obtained on a Perkin–Elmer Model 281-B spectrometer. Optical rotations were measured with a Perkin–Elmer Model 241 polarimeter. High resolution mass spectra (HRMS) were obtained on a Micromass AutoSpec. Analytical thin-layer chromatography (TLC) was performed on Merk silica gel (60F-254) plates (0.25 mm) precoated with a fluorescent indicator. Visualization was effected with ultraviolet light, potassium permanganate (0.05 M in 1 M aqueous acetic acid), and phosphomolybdic acid (7% w/v) in 95% ethanol.

3.1.1. (5*S*)-Carboxy-14-hydroxy-(3,14,15,16,17,18,19,20)-octadehydro-21-yohimbanone (1). A solution of ninhydrin (890 mg, 4.99 mmol) in 0.1N HCl (30 mL) was added to a solution of L-tryptophan (1.02 g, 4.99 mmol) in 0.1N HCl (45 mL) at ambient temperature. The resultant mixture was stirred for 48 h. The precipitate was collected by filtration and washed with cold MeOH. The crude material was recrystallized from MeOH to provide the product as a golden solid (553 mg, 32%). Mp 204°C (decomp.); $[\alpha]_D^{20}=-146$ (*c* 0.058 MeOH); R_f 0.2 MeOH/CH_2Cl_2 (15:85); ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.25 (1H, dd, $J^1=16.3$ Hz, $J^2=6.6$ Hz, $H_{6\alpha}$), 3.67 (1H, d, $J=15.6$ Hz, $H_{6\beta}$), 6.07 (1H, d, $J=5.7$ Hz, H_5), 7.03 (1H, t, 7.5 Hz, H_{17}), 7.14 (1H, t, $J=7.5$ Hz, H_{18}), 7.52–7.56 (2H, m, H_{10}, H_{16}), 7.59 (1H, d, $J=8.1$ Hz, H_{19}), 7.82 (1H, t, $J=7.6$ Hz, H_9), 7.99 (1H, d, $J=8.1$ Hz, H_8), 8.25 (1H, d, $J=7.9$ Hz, H_{11}), 9.28 (1H, br s, OH), 11.09 (1H, br s, NH), 12.95 (1H, br s, CO_2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 22.3 (C_6), 52.4 (C_5), 107.6 (C_1), 112.4 (C_{19}), 118.2/126.8 (C_{10}/C_{16}), 119.3/119.4 (C_{14}/C_{17}), 121.6 (C_8), 122.5 (C_{18}), 124.2 (C_{15}), 124.8 (C_{20}), 127.2 (C_7), 127.8 (C_{11}), 130.4 (C_3), 132.5 (C_9), 133.7 (C_2), 137.4 (C_{12}), 159.8 (CO_2H),

171.8 (C_{21}); IR (KBr) 3700–3200 (br, m), 3515 (m), 3420 (m), 3340 (m), 3060 (w), 2940 (w), 2560 (w), 1745 (m), 1645 (m), 1610 (m), 1570 (s), 1550 (s), 1490 (m), 1455 (w), 1375 (m), 1330 (m), 1280 (w), 1245 (w), 1205 (s), 1150 (m), 1125 (m), 1080 (m), 1005 (w), 970 (m), 950 (w), 775 (m), 755 (s), 705 (m) cm^{-1}; HRMS (ESI) Calcd for $C_{20}H_{14}N_2O_4$ (M^+): 346.0954, Found 346.0959.

3.1.2. (3*S*)-Carboxymethyl-1,2,3,4-tetrahydrospiro-β-carboline-1,2′-(1′,3′)-indanedione (3). A solution of ninhydrin (21.8 g, 122 mmol) in 0.1N HCl (750 mL) was added dropwise to a solution of L-tryptophan (27.0 g, 122 mmol) in 0.1N HCl (1.10 L). The resultant mixture was stirred at ambient temperature for 48 h. The yellow precipitate was collected by filtration and recrystallized from MeOH/CH_2Cl_2 to provide the product (24.8 g, 56%). Mp 162–164°C (decomp.); $[\alpha]_D^{20}=-175$ (*c* 0.270 MeOH); R_f 0.33 acetone/hexanes (30:70); ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.22 (1H, dd, J^1=15.7 Hz, J^2=11.7 Hz, $H_{4\alpha}$), 3.43 (1H, dd, J^1=15.9 Hz, J^2=4.9 Hz, $H_{4\beta}$), 3.85 (3H, s, OMe), 5.05 (1H, dd, J^1=11.4 Hz, J^2=4.8 Hz, H_3), 5.20 (1H, br s, NH), 7.10 (1H, t, *J*=7.5 Hz, H_6), 7.17 (1H, t, *J*=7.6 Hz, H_7), 7.27 (1H, d, *J*=8.1 Hz, H_8), 7.62 (1H, d, *J*=7.9 Hz, H_5), 8.17–8.29 (4H, m, $H_{4'-7'}$), 11.01 (1H, s, indole NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ 22.5 (C_4), 52.6 (C_3), 52.8 (C_{OMe}), 63.4 (C_1), 109.8 (C_{4a}), 111.7 (C_8), 118.4 (C_5), 119.6 (C_7), 122.8 (C_6), 124.6/125.0/125.2 (C_{9a}/$C_{4'}$/$C_{7'}$), 125.4 (C_{4b}), 137.0 (C_{8a}), 137.5/137.8 ($C_{5'}$/$C_{6'}$), 140.9/141.3 ($C_{3'a}$/$C_{7'a}$), 169.5 (CO_2), 193.9/194.7 ($C_{1'}$/$C_{3'}$); IR (KBr) 3164 (m), 3060 (w), 2943 (w), 2837 (w), 1742 (s), 1710 (s), 1591 (m), 1437 (m), 1345 (m), 1266 (m), 1180 (m), 1049 (m), 1024 (s), 1006 (m), 950 (m), 746 (m) cm^{-1}; HRMS (ESI) Calcd for $C_{21}H_{16}N_2O_4Na$ ($M+Na^+$): 383.1008, Found 383.1015.

Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 205934. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

3.1.3. (5*S*)-Carboxymethyl-14-hydroxy-(3,14,15,16,17,18,19,20)-octadehydro-21-yohimbanone (4). *Method A*. A solution of ninhydrin (1.78 g, 10 mmol) in 0.1N HCl (75 mL) was added dropwise to a solution of L-tryptophan (2.18 g, 10 mmol) in 0.1N HCl (75 mL) at room temperature. After complete addition, the solution was heated at reflux for 3 h. The resultant suspension was cooled to room temperature, and the precipitate was collected by filtration. Recrystallization from methanol provided the product as a yellow solid (851 mg, 24%). *Method B*. Stannous chloride dihydrate (6.27 g, 27.8 mmol) was added to a solution of **3** (5.00 g, 13.9 mmol) in MeOH (140 mL). The mixture was heated at reflux for 22 h. The yellow precipitate was collected by filtration, washing with H_2O, to provide analytically pure **4** (2.32 g, 46%). Mp 177–178°C (decomp.); $[\alpha]_D^{20}=-148$ (*c* 0.255, MeOH); R_f 0.44 MeOH/CH_2Cl_2 (5:95); ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.23–3.35 (1H, dd, J^1=16.4 Hz, J^2=6.6 Hz, $H_{6\alpha}$), 3.51 (3H, s, OMe), 3.68 (1H, d, *J*=16.5 Hz, $H_{6\beta}$), 6.19 (1H, d, *J*=5.5 Hz, H_5), 7.03 (1H, t, *J*=7.4 Hz, H_{17}), 7.15 (1H, t, *J*=7.7 Hz, H_{18}), 7.53–7.56 (2H, m, H_{10}, H_{16}), 7.60 (1H, d, *J*=8.2 Hz, H_{19}), 7.83 (1H, t, *J*=7.0 Hz, H_9), 8.01 (1H, d, *J*=8.0 Hz, H_8), 8.27 (1H, d, *J*=7.6 Hz, H_{11}), 9.33 (1H, s, OH), 11.11 (1H, s, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ 22.3 (C_6), 52.3 (C_5), 52.6 (OMe), 107.2 (C_1), 112.4 (C_{19}), 118.2/126.9 (C_{10}/C_{16}), 119.0/119.3 (C_{14}/C_{17}), 121.6 (C_8), 122.5 (C_{18}), 124.0 (C_{15}), 124.7 (C_{20}), 126.9 (C_7), 127.8 (C_{11}), 130.5 (C_3), 132.6 (C_9), 133.6 (C_2), 137.4 (C_{12}), 159.8 (CO_2Me), 170.8 (C_{21}); IR (KBr) 3429 (m), 3070 (m), 2634 (w), 1752 (s), 1647 (w), 1610 (m), 1570 (s), 1552 (s), 1482 (m), 1446 (w), 1322 (m), 1204 (s), 1143 (m), 1078 (m), 968 (w), 773 (m), 752 (s), 698 (m) cm^{-1}; HRMS (ESI) Calcd for $C_{21}H_{17}N_2O_4$ (M+H): 361.1188, Found 361.1183.

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