reaction mixture, the resulting solution was washed with dichloromethane (150 mL). The aqueous layer was acidified with concentrated hydrochloric acid (10 mL) and extracted with dichloromethane (150 mL). The extract was washed with saturated aqueous sodium chloride (60 mL). After being dried over magnesium sulfate, the solvent was evaporated under reduced pressure to give butyric acid **3** in 95% yield: mp 99.5–100.5 °C (after recrystallization from ethyl acetate); mass spectrum, m/e 185.1039 (M^+, $C_9H_{15}NO_3$); IR (KBr) 1720 (s), 1630 (s), 1210 (s) cm^{-1}; NMR ($CDCl_3$) δ 1.22 (3 H, d, J = 6.5 Hz, CH_3), 1.4–2.6 (7 H, m, aliphatic protons), 3.2–3.6 (4 H, m, aliphatic protons), 10.8 (1 H, br s, disappeared upon treatment with D_2O, COOH).

Anal. Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.15; H, 8.43; N, 7.41.

1-Methyl-$\Delta^{1(8)}$-dehydropyrrolizine (4) and Its Perchlorate (5). A mixture of butyric acid **3** (30 g) and finely powdered soda lime (30 g) was subjected to a dry distillation to afford the crude enamine **4** in quantitative yield (fraction boiling between 140 and 160 °C). Redistillation of this material under a nitrogen stream gave 14.6 g (73%) of 1-methyl-$\Delta^{1(8)}$-dehydropyrrolizidine (**4**) as a colorless oil: bp 94 °C (72 torr); mass spectrum, m/e 123.1095 (M^+, $C_8H_{13}N$), 246 (weak dimeric ion); IR (liquid film) 1710 cm^{-1} (s, enamine C=C); NMR (benzene-d_6) δ 4.40–4.53 (ca. 0.1 H, br s, vinyl proton of **4b**), 1.67 (br s, methyl protons of **4a**) [other signals (δ 0.7–3.5) appeared as complicated multiplets owing to contamination by **4b**].

To a solution of the freshly distilled enamine **4** (9.017 g, 0.073 mol) in ethanol (200 mL) was added an equivalent molar amount of perchloric acid (70%) dropwise with ice cooling. After addition of ethanol (300 mL) to the mixture, the precipitated crystals were collected by filtration, and recrystallization of the product from ethanol gave the perchlorate **5** in 88% yield as colorless flakes: mp 196–198 °C; IR (KBr) 1700 cm^{-1} (s, iminium =C=N$^+$=); NMR (pyridine-d_5) δ 3.87–4.20 (4 H, m, $^+NCH_2$), 1.9–3.7 (7 H, m, aliphatic protons), 1.20 (3 H, d, J = 7.5 Hz, CH_3).

Anal. Calcd for $C_8H_{14}ClNO_4$: C, 42.95; H, 6.30; N, 6.26. Found: C, 42.74; H, 6.58; N, 6.16.

Catalytic Hydrogenation of 4. Preparation of (±)-Heliotridane (1). A mixture of **4** (4.99 g, 0.04 mol) and platinum oxide (0.027 g) as catalyst in anhydrous ether (30 mL) was placed under a hydrogen atmosphere at atmospheric pressure. After absorption of ca. 900 mL of hydrogen, the catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. Distillation of the residue afforded 1-methylpyrrolizidine (3.375 g, 67% yield), bp 100–103 °C (108–112 torr), the IR spectrum of which was identical with that of the authentic (±)-heliotridane.[3c] Gas chromatographic analyses of this base indicated the presence of a small amount (7%) of (±)-pseudoheliotridane (**2**), possessing a retention time of 3.1 min. The picrate of this base melted at 244–247.5 °C dec.

Anal. Calcd for $C_{14}H_{18}N_4O_7$: C, 47.45; H, 5.12; N, 15.81. Found: C, 47.53; H, 5.05; N, 15.90.

Reduction of 4 with Formic Acid. Preparation of (±)-Pseudoheliotridane (2). To the enamine **4** (37.102 g, 0.302 mol) was added formic acid (27.8 g, 0.604 mol) with stirring under ice cooling. After being stirred for 1 h at room temperature, the mixture was kept at 60–70 °C for 3 h with stirring. To the mixture was added 40% aqueous sodium hydroxide (40 mL), and the resulting mixture was extracted with ether (150 mL). The ether extract was washed with saturated sodium chloride (10 mL) and dried over magnesium sulfate. After evaporation of the solvent,[9] the residue was distilled to give 1-methylpyrrolizidine (25.76 g, 68% yield) as a colorless oil, bp 80–82 °C (45 torr). The product could be resolved for satisfactory identification as authentic (±)-pseudoheliotridane.[3c] Gas chromatographic analyses of the product, however, indicated that the product contains the stereoisomer **1**, possessing a long retention time (4.1 min), in the amount of 25%. Redistillation of this sample with a microspinning-band column afforded a more purified sample of **2**, with 93.5% isomeric purity (fraction boiling at 148–150 °C). The picrate of this fraction melted at 236–238 °C dec.

Anal. Calcd for $C_{14}H_{18}N_4O_7$: C, 47.45; H, 5.12; N, 15.81. Found: C, 47.55; H, 5.20; N, 15.54.

(9) Isomeric ratio of the crude product (1:2) was 34:66 by gas chromatography.

Registry No. **1**, 17463-81-9; 1 picrate, 17463-80-8; **2**, 76548-10-2; **2** picrate, 76548-11-3; **3**, 76466-47-2; **4a**, 76466-48-3; **4b**, 76466-49-4; **5**, 76466-51-8; 2-pyrrolidinone, 616-45-5; α-methyl-γ-butyrolactone, 1679-47-6.

Improved Synthesis and Characterization of Pictet-Spengler Adducts of Phenylpyruvic Acid and Biogenic Amines

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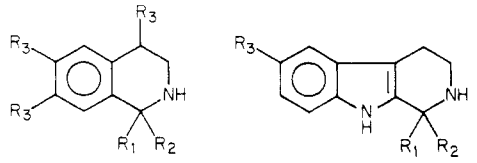
Introduction

Tetrahydroisoquinolines and β-carbolines derived from biogenic amines and from appropriate carbonyl substrates have recently attracted attention in addressing such problems as aberrant metabolism in alcoholism,[1] phenylketonuria,[2] L-dopa chemotherapy of Parkinson's disease,[3] and mental diseases such as schizophrenia.[4] A number of reports have appeared[5] describing the various physiological effects of compounds having the general features of **1** and **2**.



1 **2**

R_1 = H, CH_3, $CH_2C_6H_5$; R_2 = H, CO_2H; R_3 = H, OH, OCH_3

The Pictet-Spengler condensation of aromatic amines with aldehydes and ketones has been used extensively for the preparation of tetrahydroisoquinolines and β-carbolines.[6] We were interested in the synthesis of tetrahydroisoquinolines and β-carbolines possessing as a common feature 1,1-disubstitution by a benzyl and carboxylic acid group (**5a,b** and **7a–c**). Some of the adducts, namely, **5a** and **7a**, were described as early as 60 years ago.[7,8] Although a few 4-hydroxy-substituted tetrahydroisoquinolines have been synthesized,[6-11] the literature offers

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warnings associated with the lability of benzylic hydroxyls[11,12] which has contributed to the poor yields experienced. Furthermore loss of the benzylic hydroxyl will afford dihydroisoquinolines which have different physiological effects.[6] Several β-carboline-1-carboxylic acids have also been prepared and decarboxylated without prior rigorous proof of structure.[13,14] In this report we describe improved preparations and mass spectral and carbon-13 nulcear magnetic resonance data for a series of compounds derived from the Pictet–Spengler condensation between phenylpyruvic acid and an appropriate biogenic amine (Scheme I).

Results and Discussion

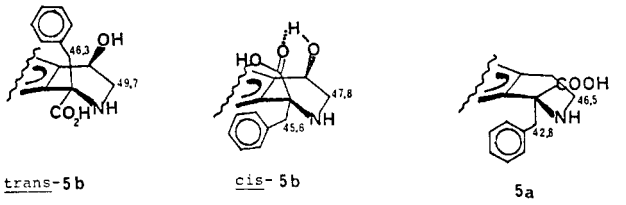
Deoxynorlaudanosolinecarboxylic acid (DNLCA), **5a**, has been prepared by the Pictet–Spengler condensation of dopamine with phenylpyruvic acid by Hahn,[7] Bobbitt,[15] and Lasala.[16] Structure elucidation was accomplished by mass spectrometry, IR, ^{1}H NMR, and derivatization.[15,16] The pH and the temperature profiles have been investigated[7] to provide optimum yields of DNLCA: pH 4.5, room temperature, 5 days;[7,15] or pH 7, 100 °C, 2 h.[16] The above conditions applied to norepinephrine and phenylpyruvic acid gave low yields of 4-hydroxy-DNLCA, **5b** (10–25%), at the expense of fragmentation at elevated temperatures or of incomplete reaction at room temperature. Following the suggestion of Williams,[11] we were able to prepare the intermediate Shiff base 8 (R = β-hydroxy-β-(3,4-dihydroxyphenyl)-ethyl) in quantitative yield by mixing norepinephrine as a free base with phenylpyruvic acid in absolute ethanol. However, exposure of 8 to reflux in acetonitrile, as suggested[11] for the adducts of norepinephrine and simple aldehydes, gave mixtures containing in excess of 16 components. Several solvents normally used for Pictet–Spengler condensation (MeOH, HOAc, DMF) gave similar results. However, exposure of 8 to Me_2SO at room temperature (4 days) or 60 °C (~8 h) gave reasonable yields of 4-hydroxy-DNLCA as a 2:1 mixture of diastereoisomers. Subsequently, we found that the same mixture could be produced from 8 in EtOH containing catalytic amounts of silica gel. When absolute ethanol was filtered through a silica gel column prior to use or when a small amount of silica gel (~1%) was added to a solution of 8 in EtOH, 4-hydroxy-DNLCA was obtained in ~85% yield (see the Experimental Section). Finally, a mixture of norepinephrine and phenylpyruvic acid in EtOH previously filtered through silica gel gave 4-hydroxy-DNLCA in 2 h at 90 °C as compared to ~8 h when untreated ethanol was used. Surface catalysis by silica gel has successfully been used in the past[17] in instances where "difficult" nucleophilic additions or substitutions required long reaction times or stringent reaction conditions.

The three β-carbolines (**7a–c**) were prepared without the above-mentioned difficulties. The ease of formation of β-carbolines from phenylpyruvic acid and tryptamine and serotonin and 5-methoxytryptamine, respectively, did not necessitate the isolation of the intermediate Schiff bases. The reactions were performed in aqueous solution at pH 6.5 and were complete in 48 h at room temperature. They could also be prepared in silica gel treated EtOH (1 h, 90 °C) with results comparable to the preparation of tetrahydroisoquinolines.

Carbon-13 NMR Spectroscopy. The tetrahydroisoquinoline carboxylic acids as well as their β-carboline counterparts proved to be extremely insoluble compounds (<5 mg/mL, H_3O^+). In order to obtain reliable chemical shift parallels, all spectra data were collected on aqueous solutions at pH 0.5. DNLCA and 4-hydroxy-DNLCA have been identified largely by the chemical shifts of aliphatic and of selected aromatic carbons, relying in part on established ^{13}C NMR assigments of isoquinoline alkaloids.[18] The regiochemical isomeric possibilities, **9** and **10**, for DNLCA have been eliminated based on the absence of coupling between H-5 and H-6 (in the ^{1}H NMR of **5a**) and of C-5 and C-6 (also absent in the ^{13}C NMR of **5a**). The ^{13}C chemical shifts of C-3 and C-4, as well as the off-resonance decoupled spectrum of **5a**, eliminated structure **10** which could, in principle, arise from a Michael-type addition to the enamine tautomer of 8.

The stereochemical assignment of 4-hydroxy-DNLCA was deduced as follows. The reaction mixture consisted of two components, roughly 2:1, of different polarities (C_{18} μBondapak, 4 and 11 min, respectively).

The major product was assigned the trans configuration based on the following observations:



The benzylic methylene in both *cis*- and *trans*-**5b** is found approximately 4 ppm downfield from its component in **5a** as a result of deshielding by either the C-4 hydroxyl (in *trans*-**5b**) or the C-1 carboxylate (in *cis*-**5b**). In the more rigid conformation of *cis*-**5b**, this methylene would experience a 1,3-interaction with the C-3 aminomethylene group. This interaction, manifested as a γ effect,[18,19] is not possible in the trans epimer. The benzylic methylene in *cis*-**5b** is shielded to the extent of 0.8 ppm. Similarly, the C-3 methylene in *cis*-**5b** resonates 1.9 ppm upfield of its trans counterpart.

Similar trends in chemical shifts are also observed for the carboxylate carbons, quaternary aromatic carbons of the benzyl substituents, and the C-4 oxygenated methines.

Furthermore, the signal of C-4 carbon in *cis*-**5b** showed enhanced intensity compared to the signal in the trans epimer. A strong hydrogen bond in *cis*-**5b** would shorten the relaxation time at C-4 and hence produce a more intense signal.[20,21]

The proof of structure of the β-carbolines was facilitated by mass spectrometry where the base peak in each case corresponded to the decarboxylated/debenzylated β-carboline nucleus. Serotonin derivative **7b** and 5-methoxytryptamine derivative **7c** were separately converted to the

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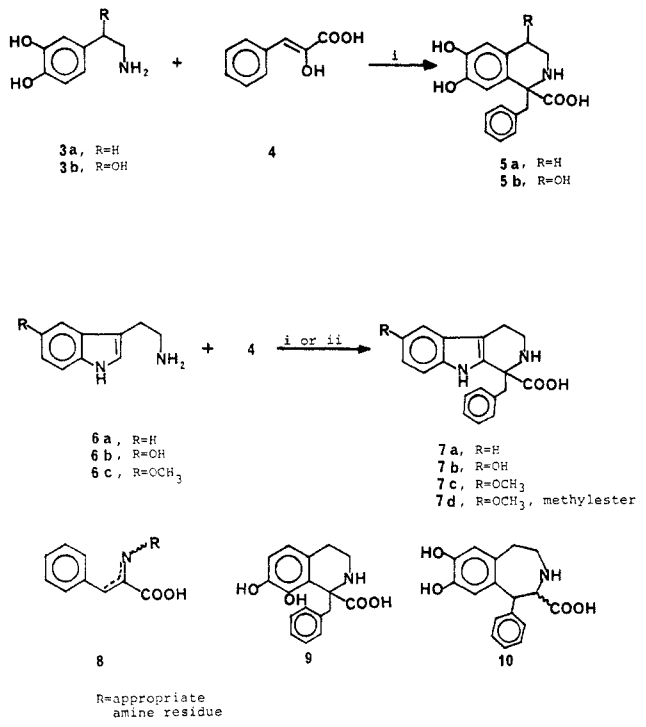
Scheme I[a]



[a] i, EtOH, 2 h, 90 °C (catalytic amount of silica gel); ii, pH 6.5, room temperature, 48 h.

methyl ester **7d** by the action of ethereal diazomethane (several exposures) and the two compounds were found to be spectrally and chromatographically identical (see the Experimental Section).

In conclusion, we have shown that simple phenethyl- or tryptophylamines smoothly afford the corresponding Pictet–Spengler products with phenylpyruvic acid. In the case of norepinephrine, where the reaction is complicated by the labile benzylic hydroxyl group and by possible lactone formation, the best results were obtained in ethanol with silica gel used as an active surface catalyst. Efforts to separate diastereoisomers of **5b** on a preparative scale are underway.

Experimental Section

Melting points were taken on a Fisher-Johns hot-stage instrument and are uncorrected. Infrared spectra were recorded by using a Pye-Unicam model spectrophotometer. Ultraviolet spectra were determined on a Heath 703 double-beam scanning spectrophotometer. ^1H and ^{13}C NMR spectra were obtained on Varian T-60 and JEOL-FX 100 instruments, respectively, using tetramethylsilane or 2,2-dimethyl-2-silapentane-5-sulfonate as an internal standard. Mass spectra were recorded on LKB-9000, Du Pont 20-491 (low resolution) and Du Pont 21-110C (high resolution) mass spectrometers. High-pressure liquid chromatography was carried out in the reverse phase (C_{18} μBondapak, Waters Associates) with specified solvents. All reactions except those performed in aqueous solutions were carried out in an inert atmosphere. All chemicals were Sigma products used without further purification.

6,7-Dihydroxy-1-benzyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic Acid (5a). Dopamine hydrochloride (100 mg, 0.5 mmol), phenylpyruvic acid (90 mg, 0.55 mmol), and sodium carbonate (50 mg, 0.5 mmol) were mixed in 2 mL of absolute ethanol, and the solution was gassed with nitrogen. The mixture was heated at 80 °C in a *closed* screw-cap test tube. During this time, a heavy white precipitate deposited out of a yellowish solution. The cooled mixture was filtered, and the crystals were washed with water, ethanol, and ethyl ether and dried to give 138 mg (92%) of (**5a**), mp 238–245 °C dec. Recrystallization from MeOH–HCl (2:1) gave the hydrochloride: mp 240–244 °C dec (lit[2b,15] 240 °C dec.); IR (Nujol) 3400, 3200, 1620 cm^{-1}; ^1H NMR (D_2O/H_2SO_4) δ 7.2–7.4 (m), 6.74 (s), 3–4 (m); ^{13}C NMR (D_2O/H_2SO_4) δ 26.7 (t), 42.8 (t), 46.5 (t), 68.9 (s) 117.9 (d), 118.4 (d), 123.9 (s), 127.5 (s), 131.3 (d), 131.9 (d), 132.9 (d), 134.8 (s), 145.9 (s), 147.7 (s), 173.7 (s); mass spectrum (70 eV, relative intensity), *m/e* 299 (M^+, 2), 254 (25), 252 (22), 208 (50), 164 (68), 162 (45), 132 (20), 91 (100), 77 (20), 65 (30); high resolution mass spectrum (EI) showed M^+, 299.1152 (calcd for $C_{17}H_{17}NO_4$ 299.1157).

***cis*- and trans-4,6,7-Trihydroxy-1-benzyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic Acid (5b). A. Via Schiff Base 8.** Norepinephrine (85 mg, 0.5 mmol) and phenylpyruvic acid (90 mg, 0.505 mmol) were mixed in 2 mL of absolute ethanol and gassed with nitrogen. Brief heating (80 °C, 20 s) was required to dissolve all the solids. In a few minutes, a gel formed which crystallized on standing at room temperature overnight. The crystals were collected by filtration, washed with ethanol and ether, and dried to give 154 mg (97.5%) of white crystals (*E/Z* mixture of 8):[22] mp >170 °C dec; IR (Nujol) 3550, 3500, 3300, 3100, 1625 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 6.2–7.8 (m), 4.5–4.8 (m), 2.4–3.2 (m); mass spectrum (70 eV, relative intensity), *m/e* no M^+, 253 (40), 252 (80), 236 (25), 174 (20), 164 (58), 146 (11), 120 (40), 103 (35), 102 (40), 91 (100), 77 (38), 74 (40); high-resolution mass spectrum (EI) did not show M^+ but gave M – H_2O 297.0995 (calcd for $C_{17}H_{15}NO_4$ 297.1001), M – (H_2O + CO_2 + H), 252.1029 (calcd for $C_{16}H_{15}NO_2$ 252.1024).

The Schiff base (10 mg) was dissolved in Me_2SO (1 mL) and the mixture gassed with nitrogen. It was then heated in a closed, screw-cap test tube at 60–80 °C for 2 h. After cooling in ice, the mixture was poured into cold water. The precipitate was collected, washed with ethanol and ether, and dried to give 2 mL (90%) of **5b** as a 2:1 mixture of stereoisomers: mp >220 °C dec; $[\alpha]^{20}_D$ + 460 (*c* 0.25, H_2O, H_2SO_4); IR (Nujol) 3500, 1650, 1620, 1580 cm^{-1}; ^1H NMR (D_2O/H_2SO_4) δ 7.1–7.4 (m), 6.9–7.0 (br d), 3–4 (m); ^{13}C NMR (D_2O/H_2SO_4) δ (trans) 46.3 (t), 49.7 (t), 64.5 (d), 69.2 (s), 117.9 (d), 119.2 (d), 123.5 (s), 128.6 (s), 131.9 (d), 132.9 (d), 134.4 (d), 134.7 (s), 147.9 (s), 147.9 (s), 172.9 (s); ^{13}C NMR (D_2O/H_2SO_4) δ (cis) 45.6 (t), 47.8 (s), 64.3 (d), 172.9 (s); mass spectrum (70 eV, relative intensity), *m/e* 253 (40), 252 (85), 236 (25), 224 (4), 206 (8), 164 (32), 162 (30), 102 (30), 91 (100), 77 (22), 65 (30); high-resolution mass spectrum (EI) did not show M^+ but gave M – (H_2O + CO_2 + H) 252.1024 (calcd for $C_{16}H_{14}NO_2$ 252.1024).

B. Direct Preparation. Absolute ethanol was filtered through a short column of silica gel (EM reagent, 0.5–0.2 mm) and 85 mg of norepinephrine and 90 mg of phenylpyruvic acid were added. The mixture was gassed with nitrogen and heated at 90 °C in a closed, screw-cap test tube for 2 h. The cooled mixture was triturated with ether and the filtered yellowish crystals were packed well on a fritted-glass funnel and washed with 2 mL of ice-cold 0.1 N HCl. The resulting white powder was washed with ethanol and ether and dried to give 140 mg (88%) of **5b** as a mixture of cis and trans epimers (1:2 by high-pressure LC on C_{18} μBondapak, 11 and 4 min, respectively, in H_2O–EtOH–HOAc (90:10:1) at a flow rate of 2 mL/min).

General Method of Preparation of 1,1-Disubstituted β-Carbolines. Phenylpyruvic acid (175 mg, 1.05 mmol) and the appropriate amine (1 mmol) were dissolved in 3.5 mL of absolute ethanol *or* in 5 mL of pH 6.5 buffer. The solution was allowed to stand for 48 h, and the crystals were collected by filtration, washed with water, acetone, and ether and dried. In this manner the following compounds were obtained.

1-Benzyl-1,2,3,4-tetrahydro-β-carboline-1-carboxylic acid (7a): obtained as hydrochloride (from tryptamine hydrochloride); 335 mg (94%); mp >230 °C dec; IR (Nujol) 3450, 3400, 3100, 1635 cm^{-1}; ^1H NMR (CF_3COOD) δ 3.1 (br s, 2 H), 3.6 (br m, 4 H), 7.1 (br s, 9 H); mass spectrum (70 eV, relative intensity), *m/e* 306 (M^+, 0.5), 292 (1), 262 (20), 215 (100), 171 (35), 169 (46), 115 (35), 91 (95), 65 (30); high-resolution mass spectrum (EI) showed M^+,

(22) We attempted to obtain a ^{13}C NMR spectrum of 8 but were unsuccessful. Schiff base 8 decomposed to **5b** in Me_2SO at room temperature, doubling the number of signals in the spectrum. Subtraction techniques would yield *some* but not all signals corresponding to 8. From these results it was evident that 8 was a ~2:1 mixture of *E/Z* stereoisomers of tautomeric forms. Further proof of the Schiff base structure comes from quantitative titration with aqueous acid to its original constituents as demonstrated by high-pressure LC.

306.1371 (calcd for $C_{19}H_{18}N_2O_2$ 306.1368).

1-Benzyl-1,2,3,4-tetrahydro-8-hydroxy-β-carboline-1-carboxylic acid (7b): from serotonin oxalate; 290 mg (90%); mp >230 °C dec; IR (Nujol) 3580, 3500, 3400, 3100, 1622 cm^{-1}; ^1H NMR (CF_3COOD) δ 3.1 (br s, 2 H), 3.8 (br m, 4 H), 7.1 (m) and 7.4 (m) (total integration 8 H); mass spectrum (70 eV, relative intensity), *m/e* no M^+, 278 (10), 231 (8), 187 (100), 146 (30), 133 (50), 117 (12), 91 (40), 65 (18); high-resolution mass spectrum (EI) showed weak M^+ and M - CO_2, 278.1414 (calcd for $C_{18}H_{18}N_2O$ 278.1419).

1-Benzyl-1,2,3,4-tetrahydro-8-methoxy-β-carboline-1-carboxylic acid (7c): from 5-methoxytryptamine; 315 mg (93%); mp 225 °C dec; IR (Nujol) 3400, 3100, 2400, 1635, 1595 cm^{-1}; ^1H NMR (CF_3CO_2D) 3.2 (m, 2 H), 3.8 (m, 2 H), 3.9 (br s, 2 H), 4.05 (s, 3 H), 7.1-7.6 (m, 8 H); mass spectrum (70 eV, relative intensity), *m/e* no M^+, 292 (15), 290 (25), 289 (27), 245 (44), 201 (100 at lower voltages), 199 (10), 145 (20), 123 (35), 91 (100), 65 (40); high-resolution mass spectrum (EI) did not show M^+ but gave M - (H_2O + H), 317.1289 (calcd for $C_{20}H_{17}N_2O_2$ 317.1278).

Derivatization of β-Carbolines. Either **7b** or **7c** (100 mg) was dissolved in MeOH/HCl (2:1) (20 mL) and added to ethereal diazomethane (from 1 g of nitrosomethylurea). After standing at room temperature for 24 h the oil was taken up in 10 mL of MeOH and the process repeated 3-4 times. In this way we obtained 8-methoxy-1-(carbomethoxy)-β-carboline **7d**, the ^{13}C NMR spectrum of which showed the following signals:[23] ($CDCl_3$) δ 26.2 (t), 44.3 (t), 55.5 (q), 55.8 (q), 61.7 (t), 62.2 (s), 100. 3 (d), 111.2 (d), 112.3 (d), 112.4 (s), 126.5 (s), 127.8 (d), 128.2 (s), 128.5 (s), 129.9 (d), 131.6 (s), 136.1 (s) 153.9 (s), 172.0 (s); mass spectrum (70 eV, relative intensity), *m/e* 350 (M^+, 4), 291 (50), 290 (50), 289 (49), 259 (100), 201 (92), 173 (88), 160 (62), 91 (68).

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Registry No. **3a**·HCl, 62-31-7; **3b**, 51-41-2; **4**, 127-17-3; **5a**, 57256-22-1; **5a**·HCl, 76480-17-6; *cis*-**5b**, 76480-18-7; *trans*-**5b**, 76480-19-8; **6a**·HCl, 343-94-2; **6b** oxalate, 3036-16-6; **6c**, 608-07-1; **7a**, 17952-61-3; **7b**, 17994-22-8; **7c**, 29573-13-5; **7d**, 76480-20-1; (*E*)-**8**, 76480-21-2; (*Z*)-8, 76480-22-3.

(23) ^{13}C NMR assignments for **7d** are in agreement with a recent study of related 3-(methoxycarbonyl)tetrahydro-β-carbolines.[24] Due to their poor solubility, however, it proved impossible to obtain ^{13}C NMR spectra for the free acids **7a-c**.

(24) Ungemach, F.; Soerens, D.; Weber, R.; DiPierro, M.; Campos, O.; Mokry, P.; Cook, J. M.; Silverton, J.V. *J. Am. Chem. Soc.* **1980**, *102*, 6976. Soerens, D.; Sandrin, J.; Ungemach, F.; Mokry, P.; Wu, G. S.; Yamanaka, E.; Hutchins, L.; DiPierro, M.; Cook, J. M. *J. Org. Chem.* **1979**, *44*, 535.

Neophotosantonin: A [1,5] Hydrogen Shift Isomer of Photosantonin[1]

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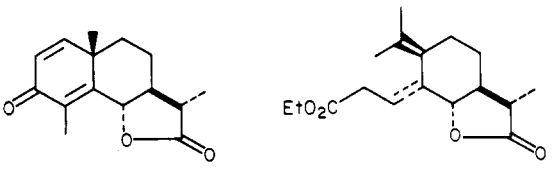
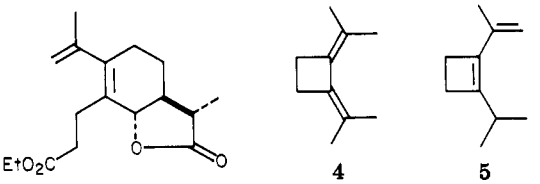
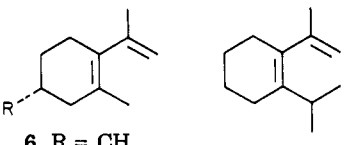
The sesquiterpene α-santonin (**1**), which has proved to be valuable as a chiral synthon,[2] is a well-known prototype of 2,5-cyclohexadienone photochemistry. When exposed to sunlight or irradiated through Pyrex, a neutral solution of **1** in ethanol yields the dienoid ester photosantonin (**2**).[3] Because of its structure, the crowded diene system in **2** is highly twisted (dihedral angle +64° by X-ray crystallography[4]) and is therefore of particular interest in connection with the optical rotatory properties of nonplanar conjugated dienes.[5] For this same reason, although **2** has long been regarded as "the ultimate product"[3a] of this photolysis of **1**, its further photorearrangement under more energetic irradiation into the isomeric structure **3** by an antarafacial [1,5] sigmatropic hydrogen shift should be sterically favored and is now reported. A close analogy for this transformation is the photoisomerization at 254 nm of 1,2-diisopropylidenecyclobutane (**4**) to 1-isopropenyl-2-isopropylcyclobutene (**5**).[6]



1 **2**



3 **4** **5**



6, R = CH_3
7, R = H **8**

Best results in the formation of **3**, for which the name "neophotosantonin" is proposed,[7] were obtained by irradiation of **2** in ethanol through a Vycor filter or of **1** in ethanol directly with a quartz-jacketed mercury-vapor lamp. Because of the sensitivity of **3** to further photolysis under these conditions, it was important to avoid overirradiation. In contrast to **2**, which is levorotatory and forms irregular plates, mp 67-68 °C, **3** is dextrorotatory and crystallizes in fine, thin needles, mp 74-75 °C. No evidence for rearrangement of **2** to **3** simply by heating could be detected. Evidently **2**, unlike **4**,[6] is sterically prevented from undergoing the suprafacial process required for a concerted thermal [1,5] sigmatropic hydrogen shift.[8]

(1) Presented before the Division of Organic Chemistry at the 181st National Meeting of the American Chemical Society, Atlanta, GA., Mar 29-Apr 3, 1981; ORGN 165.

(2) For recent applications, see: Edgar, M. T.; Greene, A. E.; Crabbé, P. *J. Org. Chem.* **1979**, *44*, 159-160; Greene, A. E. *J. Am. Chem. Soc.* **1980**, *102*, 5337-5343; Fujimoto, Y.; Miura, H.; Shimizu, T.; Tatsuno, T. *Tetrahedron Lett.* **1980**, *21*, 3409-3412.

(3) For review, see: (a) Kropp, P. J. *Org. Photochem.* **1967**, *1*, 2-4 ff. (b) Schaffner, K.; Demuth, M. In "Rearrangements in Ground and Excited States"; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. 3, pp 281-282ff.

(4) Determination in the laboratory of Professor B. Lee, University of Kansas; to be published.

(5) Burgstahler, A. W.; Barkhurst, R. C.; Gawroński, J. K. In "Modern Methods of Steroid Analysis"; Heftmann, E., Ed.; Academic Press: New York, 1973; Chapter 16. Cf.: Moriarty, R. M.; Paaren, H. E.; Weiss, U.; Whalley, W. B. *J. Am. Chem. Soc.* **1979**, *101*, 6804-6810.

(6) Kiefer, E. F.; Tanna, C. H. *J. Am. Chem. Soc.* **1969**, *91*, 4478-4480.

(7) This name is suggested because the term "isophotosantonic lactone" already designates a structurally very different compound produced by acid-catalyzed photolysis of **1**.[3]

(8) Cf.: Spangler, C. W. *Chem. Rev.* **1976**, *76*, 187-217; McCullough, J. J. *Acc. Chem. Res.* **1980**, *13*, 270-276.

0022-3263/81/1946-1741$01.25/0