The Amine Addition Products of Pseudoascaridole

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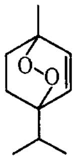
Ascaridole (**1**), the main constituent of chenopodium oil, undergoes thermal rearrangement to yield pseudoascaridole, an isomeric *cis*-diepoxide (**2**).[1] Thoms and Dobke[2] treated pseudoascaridole with aqueous ammonia and methylamine and assigned structures **5a** and **5b**, respectively, to the resulting products. This paper presents data indicating that the correct structures for these amino alcohols are represented by **3a** and **3b**. The product resulting from the reaction of aqueous ammonia and pseudoascaridole (**3a**) was recovered unchanged after 5-hr reflux with 5% HCl. The infrared spectrum of **3a** showed the presence of two hydroxyl groups (two resolved strong peaks at 3230 and 3350 cm^{-1}) while the nmr spectrum showed two one-proton doublets at τ 6.30 and 6.45 with coupling constants of 9 ± 1 Hz. The position of these doublets is indicative of the CH(OH)-CH(OH) structure and the large J value confirms the *cis* configuration of the hydroxyls at C-2 and C-3. Treatment of **3a** with acetyl chloride gave the diacetate hydrochloride **4**. The infrared spectrum of the latter compound showed no absorption in the 3100–3700 cm^{-1} region but had a strong carbonyl band at 1730 cm^{-1}. The product resulting from the reaction of methylamine and pseudoascaridole, **3b**, had a strong peak in the infrared at 3400 cm^{-1} and two one-proton doublets at τ 6.17 and 6.51 with coupling constants of 8 ± 1 Hz.



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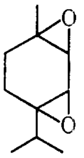

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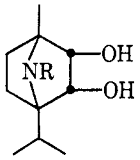
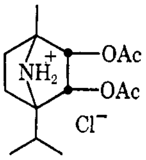


3a, R = H
b, R = CH$_3$



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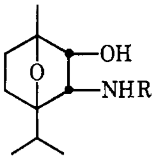
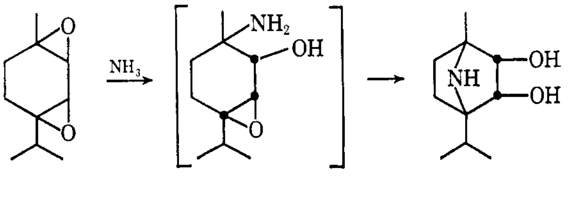


5a, R = H
b, R = CH$_3$

The structures of the amine addition products can be rationalized by the following reactions which involve an initial attack of the amine at C-1 (or C-4) followed by an internal attack of nitrogen at C-4 (or C-1). While



the initial attack of nitrogen at a tertiary carbon seems unlikely on steric grounds, it is consistent with the observation that basic hydrolysis of **2** yields the all-*trans* p-menthane-1,2,3,4-tetrol (**6**).[1a]

Experimental Section[3]

Pseudoascaridole (2).—Ascaridole was isomerized according to the procedure described by Nelson.[4] The pseudoascaridole was purified by distillation; bp 70–73° (0.5 mm).

1,4-Imino-*p*-menthane-2,3-diol (3a).—Pseudoascaridole and 25% NH_4OH were heated at 125° in a sealed tube for 5 hr. The reaction mixture was extracted with ether. The ethereal solution was dried and concentrated to yield 1,4-imino-p-menthane-2,3-diol, mp 141°; nmr (8% $CDCl_3$) τ 6.30 (d, 1, J = 9 Hz), 6.45 (d, 1, J = 9 Hz), 7.9–8.3 (m, 5), 8.75 (s, 3), 9.0 (d, 3, J = 7 Hz), 9.1 (d, 3, J = 7 Hz), and a three-proton peak whose position was concentration dependent; ir (Nujol) 3230 and 3350 cm^{-1} (COH).

1,4-Imino-*p*-menthane-2,3-diacetoxy hydrochloride (4) was prepared by adding acetyl chloride to compound **3a**. Recrystallization of the crude product from chloroform–petroleum ether C afforded the hydrochloride, mp 237–238°; ir (Nujol) 1730 cm^{-1} (O=C—O), no absorption between 3700 and 3100 cm^{-1}.

Anal. Calcd for $C_{14}H_{24}O_4NCl$: C, 54.98; H, 7.91. Found: C, 54.58; H, 7.84.

N-Methyl-1,4-imino-*p*-menthane-2,3-diol (3b).—A mixture of 16 g of pseudoascaridole and 13 g of absolute alcohol containing 4 g of methylamine was heated in a sealed tube at 125–130° for 12 hr.

The ethanol was removed by evaporation and the residue was recrystallized from petroleum ether C-chloroform to yield a white solid, mp 156.5–157.0°; nmr (8% $CDCl_3$) τ 6.17 (d, 1, J = 8 Hz), 6.51 (d, 1, J = 8 Hz), 7.5–8.7 (m, 5), 8.8 (s, 3), 9.00 (d, 3, J = 7 Hz) 9.02 (d, 3, J = 7 Hz), and a two-proton peak whose position was concentration dependent; ir (Nujol) 3400 cm^{-1} (COH).

Registry No.—**3a**, 20797-85-7; **3b**, 20817-02-1; **4**, 20797-86-8.

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(1) (a) O. A. Runquist, Ph.D. Thesis, University of Minnesota, July 1956, pp 20–46; *Dissertation Abstr.*, **16**, 2313 (1956). (b) J. Boche and O. Runquist, *J. Org. Chem.*, **33**, 4285 (1968).

(2) H. Thoms and W. Dobke, *Arch. Pharm.*, **268**, 128 (1930).

(3) Melting points are uncorrected.

(4) E. K. Nelson, *J. Amer. Chem. Soc.*, **33**, 1404 (1911).

Knoevenagel Condensation in the Homophthalic Acid Series. A Synthesis of Zearalenone

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The homophthalic acid system is formally an aromatic analog of malonic acid and might consequently be expected to function in some measure in a Knoevenagel condensation with resultant loss of carbon dioxide and water.[1]

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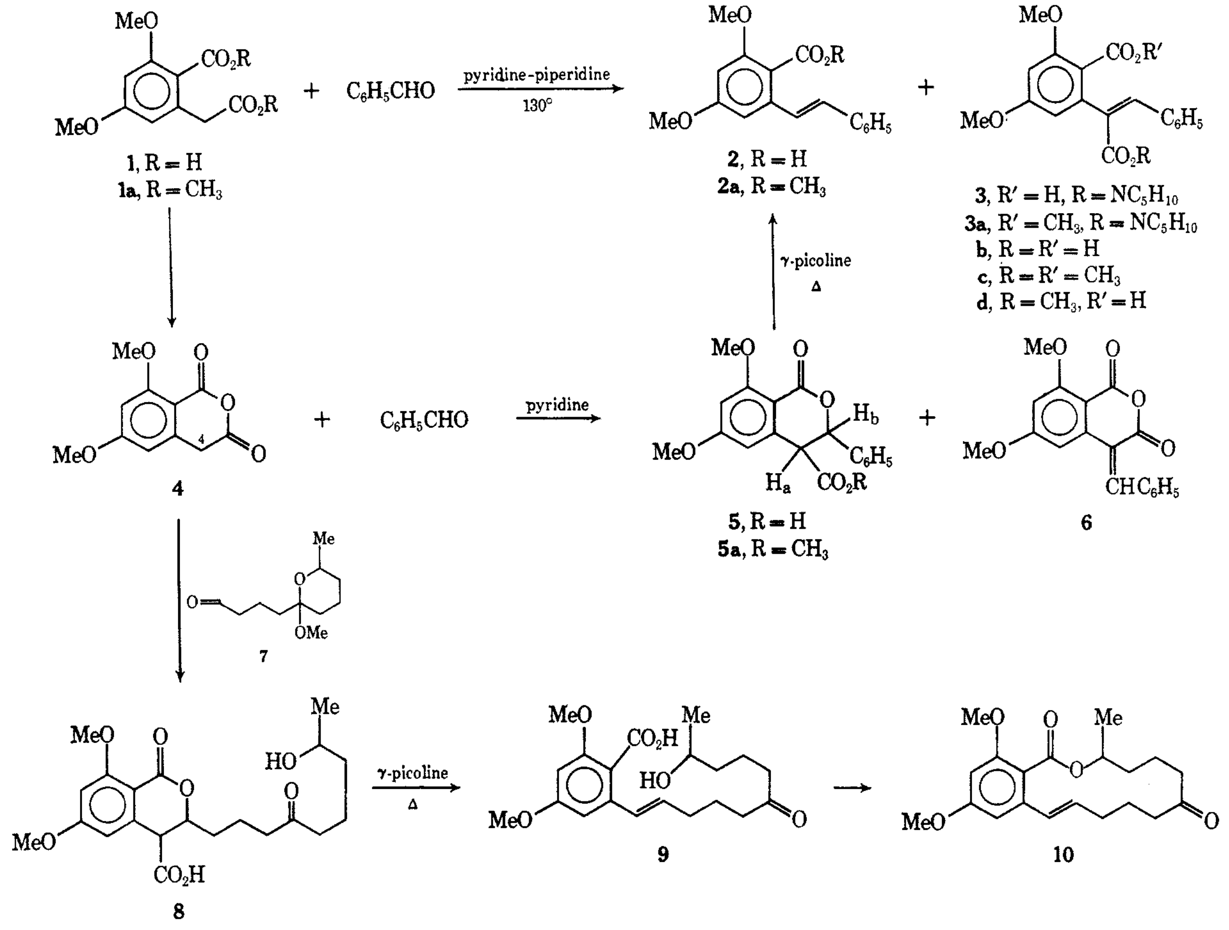
(1) For a recent review of the Knoevenagel reaction, see G. Jones, *Org. Reactions*, **15**, 204 (1967).



Benzaldehyde was observed to condense with 3,5-dimethoxyhomophthalic acid (**1**) in refluxing pyridine containing piperidine to yield the Knoevenagel product **2** as the major component together with a minor amount of aldolization product as its amide derivative **3**. In the absence of piperidine, the minor component formed appeared as the free diacid **3b**. Under the above conditions, the diester **1a** underwent little or no condensation.

By employing the anhydride **4** as the donor component together with benzaldehyde, condensation in pyridine occurred rapidly at room temperature. The inordinate lability of the C_4 protons of **4** was demonstrated by their rapid exchange with deuterium in pyridine–D_2O solution. The product from the condensation of **4** with benzaldehyde was largely a diastereoisomeric mixture of lactonic acids **5**. The latter could be decarboxylated in hot γ-picoline to produce the Knoevenagel product obtained from the diacid condensation, namely, **2**. Alternatively, esterification of **5** with diazomethane followed by hydrolysis with 1 equiv of alkali provided the half-ester **3d** related to the minor product in the diacid series.

Condensation of the anhydride **4** with γ-(2-methoxy-6-methyltetrahydropyran-2-yl)butyraldehyde (**7**) produced, in analogy with the benzaldehyde case, a crude mixture of lactonic acids[2] formulated as **8**. The latter, in hot γ-picoline, was converted to the known seco acid **9** derived from zearalenone, which in turn was converted to *dl*-zearalenone dimethyl ether **10** by trifluoroacetic anhydride in benzene.[3]

Experimental Section

Reaction of 3,5-Dimethoxyhomophthalic Acid with Benzaldehyde. A. In Pyridine with Piperidine Catalysis.—A mixture of 0.841 g (0.0035 mol) of 3,5-dimethoxyhomophthalic acid[4] and 0.743 g (0.007 mol) of benzaldehyde in 1.4 ml of dry pyridine containing three drops of piperidine was heated at 80–90° for 1 hr and then at 125–130° for 17 hr in a nitrogen atmosphere. The cooled reaction mixture was made acidic with dilute hydrochloric acid and extracted with chloroform. The organic layer was extracted several times with 5% sodium bicarbonate, and the alkaline layers were combined, made acidic, and extracted with chloroform. The chloroform layer was washed with water, dried over anhydrous sodium sulfate, and evaporated to yield 0.851 g of gummy material. The latter, on standing in an acetone–ether mixture, deposited 0.202 g of crystalline **3**, recrystallized from methanol to mp 212–216°; ir (Nujol) 3.0–4.0, 5.84, 6.14 μ; λ_{max}^{MeOH} 277.5 mμ (ε 18,600).

Anal. Calcd for $C_{23}H_{25}O_5N$: N, 3.54. Found: N, 3.40.

Methyl Ester 3a was obtained by treatment of **3** with diazomethane; mp 147–149° (ether–petroleum ether, bp 30–60°); ir ($CHCl_3$) 5.84 and 6.15 μ; λ_{max}^{MeOH} 280 mμ (ε 20,200); nmr ($CDCl_3$) δ 1.01–1.75 (m, 6 H), 3.72, 3.78, 3.82 (each s, 3 OCH_3), 6.31, 6.48 (each br d, 2 H), 7.22 (s, 5 H), and 7.81 (s, 1 H). The signal due to the two methylenes adjacent to nitrogen of the piperidine moiety was partially obscured by the signals due to the methoxyl hydrogens.

Anal. Calcd for $C_{24}H_{27}O_5N$: C, 70.40; H, 6.65; N, 3.42. Found: C, 70.01; H, 6.58; N, 3.41.

A sample (0.607 g) of the noncrystalline residue from the isolation of **3** was chromatographed (dry column technique) on 50 g of silica gel H and eluted with chloroform–ethyl acetate–acetic

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(2) For a preliminary account of this work, see N. N. Girotra and N. L. Wendler, *Chem. Ind.* (London), 1493 (1967).

(3) D. Taub, N. N. Girotra, R. D. Hoffsommer, C. H. Kuo, H. L. Slates, S. Weber, and N. L. Wendler, *Tetrahedron*, **24**, 2443 (1968).

(4) H. L. Slates, S. Weber, and N. L. Wendler, *Chimia*, 468 (1967).

acid (50:40:5). Initial fractions afforded a small amount of benzoic acid; succeeding fractions[5] on crystallization from ether–petroleum ether afforded 0.300 g of **2**, mp 121–123°; ir ($CHCl_3$) 2.8–4.1, 5.81, 5.91 (the two carbonyl bands due to monomeric and dimeric forms), 6.12, and 10.38 μ; λ_{max}^{MeOH} 300 (ε 27,900), 242.5 (ε 14,300), 232.5 (ε 16,400), and 225 (ε 18,000); nmr ($CDCl_3$) δ 3.88 (s, 2 OCH_3), 6.45, 6.81 (each d, *J* = *ca.* 2.5 cps, 2 H), 7.45 (br m, 7 H), and 10.85 (s, 1 H, exchanges with D_2O).

Anal. Calcd for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 72.01; H, 5.65.

Methyl ester 2a was obtained by treatment of the acid **2** with diazomethane; mp 74–76° (ether–petroleum ether); ir ($CHCl_3$) 5.81, 6.10, and 10.38 μ; uv λ_{max}^{MeOH} 299 (ε 27,900), 242.5 (ε 14,700), 232.5 (ε 16,300), and 218 mμ (ε 18,800); nmr ($CDCl_3$) δ 3.81, 3.85, 3.91 (each s, 3 OCH_3), 6.41, 6.78 (each d, *J* = 2 cps, 2 H), 7.08 (s, 2 H), and 7.38 (m, 5 H).

Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.46; H, 6.08. Found: C, 72.70; H, 5.81.

B. In Pyridine.—Treatment of 0.841 g of 3,5-dimethoxyhomophthalic acid with 0.743 g of benzaldehyde in 1.4 ml of dry pyridine under the conditions described above gave 0.794 g of sodium bicarbonate soluble material. Dry column chromatography of the latter on 75 g of silica gel H and elution with chloroform–ethyl acetate–acetic acid (55:50:5), followed by crystallization of pertinent fractions, gave (1) 0.360 g (ether–petroleum ether) of **2**, mp 121–123°, identical with material obtained by procedure A; and (2) 0.050 g of **3b**, mp 184–188° (acetone–hexane); ir (Nujol) 3.0–4.0, 5.86, 5.98, and 6.24 μ.

Dimethyl ester **3c** was obtained by treatment of **3b** with diazomethane; mp 136–137° (acetone–hexane); ir ($CHCl_3$) 5.82, 5.84, and 6.14 μ; uv λ_{max}^{MeOH} 280 mμ (ε 20,200); nmr ($CDCl_3$) δ 3.70, 3.72, 3.78, 3.89 (each s, 4 OCH_3), 6.28, 6.54 (each br d, *J* = *ca.* 2.5 cps, 2 H), 7.19 (br s, 5 H), and 7.81 (s, 1 H).

Anal. Calcd for $C_{20}H_{20}O_6$: C, 67.40; H, 5.66. Found: C, 67.19; H, 5.53.

Reaction of 3,5-Dimethoxyhomophthalic Anhydride with Benzaldehyde.—To a mixture of 0.889 g of 3,5-dimethoxyhomophthalic anhydride[4] and 0.849 g of benzaldehyde was added 1.8 ml of dry pyridine. After stirring for 5 hr at room temperature, the reaction mixture was diluted with water and extracted with chloroform. The chloroform layer was in turn washed with dilute hydrochloric acid, saturated sodium bisulfite, and finally 5% sodium bicarbonate to give, after evaporation of the solvent, 0.108 g of neutral material. From the bicarbonate extract was obtained 1.034 g of acidic material. The neutral material, on three crystallizations from acetone–hexane, gave yellow **6**, mp 162–166°; ir ($CHCl_3$) 5.63 and 5.76 μ.

Anal. Calcd for $C_{18}H_{14}O_5$: C, 69.67; H, 4.55. Found: C, 69.47; H, 4.41.

Treatment of **6** with dilute sodium hydroxide furnished **3b**. Since the acidic material resisted purification either by crystallization or by dry column chromatography, a sample (0.325 g) recovered from chromatography was treated with excess diazomethane. The dry column chromatography of the resulting gummy material on 25 g of silica gel H and elution with chloroform–ethyl acetate (90:35) led to the isolation of 0.164 g of single-spot material which was a mixture of *trans* and *cis* isomers of **5a** in the ratio of *ca.* 65:35, respectively, as indicated by nmr. The signals due to hydrogens of methoxyl groups in the two isomers appeared very close to one another at δ 3.83, 3.86, 3.92, and 3.93. However, carbomethoxyl hydrogens in the *cis* and *trans* isomers gave well-separated signals at δ 3.45 and 3.67 in the ratio of 35:65, the former peak appearing at higher field due to the shielding effect of the *cis*-oriented monosubstituted phenyl group. Methine H_a exhibited a signal comprised of two doublets of unequal intensities at δ 4.04 (*J* = *ca.* 3.5 cps) and 4.22 (*J* = *ca.* 8.0 cps); the former was less intense and was ascribed to the *cis* isomer on the basis of small coupling constants, as expected from the dihedral angle between *cis* H_a and H_b. Further confirmation of the structures **5** and **5a** was obtained by the following two experiments.

Treatment of 5a with Aqueous Sodium Hydroxide.—A solution of 0.158 g of **5a** in 4.65 ml of 0.1 *N* sodium hydroxide and 10 ml of methanol was allowed to stand at room temperature, heated on a steam bath for 0.5 hr, and evaporated to remove methanol. The solution was extracted with ethyl acetate, made acidic with dilute hydrochloric acid, and extracted with chloroform to give 0.152 g of pratially crystalline acidic material which on crystallization twice from acetone–ether furnished 0.115 g of **3d**, mp 138–141°; ir ($CHCl_3$) 2.80–4.0 (br), 3.10, 5.80, 5.86, and 6.15 μ; λ_{max}^{MeOH} 279 mμ (ε 20,300); nmr ($CDCl_3$) δ 3.69, 3.73, 4.04 (each s, 3 OCH_3), 6.32, 6.58 (each br d, 2 H), 7.13 (m, 5 H), 7.78 (s, 1 H), and 9.97 (br, 1 H exchange with D_2O).

Anal. Calcd for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30. Found: C, 66.37; H, 5.37.

Treatment of a small amount of **3d** in methanol with ethereal diazomethane furnished **3c**.

Treatment of 5 with γ-Picoline.—A solution of 0.150 g of crude **5** in 1 ml of γ-picoline was heated at *ca.* 145° for 8 hr under an atmosphere of nitrogen. After dilution with water, the cooled reaction mixture was acidified with dilute hydrochloric acid and extracted with 5% sodium bicarbonate to give, on acidification of the bicarbonate extract, 0.036 g of **2** (single spot), mp 121–123° (ether–petroleum ether).

γ-(2-Methoxy-5-methyltetrahydropyran-2-yl)butyraldehyde (7).—A slow stream of 3% ozone was passed through a solution of 3.966 g of 2-(pent-4-enyl)-2-methoxy-6-methyltetrahydropyran[3] in 50 ml of ethyl acetate at *ca.* −60° until the reaction mixture was saturated with ozone. The excess ozone was removed by a stream of nitrogen and the solution was added at room temperature to 0.792 g of 10% Pd–C and 0.792 g of 5% Pd–$CaCO_3$, presaturated with hydrogen, in 50 ml of ethyl acetate. The addition was accompanied by evolution of heat. The reaction mixture was cooled to room temperature and stirred in a hydrogen atmosphere for 1.5 hr. At the end of this time, a negative test for peroxide was registered. After removal of the catalyst by filtration, the filtrate was evaporated at room temperature; the residue was dissolved in petroleum ether, washed with 5% sodium bicarbonate, dried (Na_2SO_4), and evaporated to give 3.85 g of **7** as an oil, ir (film) 3.73 and 5.80 μ; nmr (CCl_4) δ 1.08 (d, *J* = 6.5 cps, CH_3-CH-), 3.13 (s, OCH_3), and 9.75 (t, HC=O). The nmr spectrum underwent a change within a short time, thus indicating the labile nature of the aldehyde, which, therefore, was used in the following experiment without further purification.

(±)-Zearalenone Dimethyl Ether (10).—A solution of 0.556 g of 3,5-dimethoxyhomophthalic anhydride (**4**) and 0.751 g of **7** in 5 ml of pyridine was stirred at room temperature for 4 hr. At the end of this period, the reaction mixture was diluted with water, made acidic with dilute hydrochloric acid, and extracted with chloroform. The organic layer was extracted several times with 5% sodium bicarbonate. The alkaine extracts were made acidic and on extraction with chloroform furnished 0.474 g of crude amorphous material, ir ($CHCl_3$) 2.80–4.10, 5.84, and 6.23 μ; nmr ($CDCl_3$) δ 1.15, 1.22 (each d, *J* = *ca.* 6.5 cps, CH_3–CH–) (multiplicity of the signal changed to a doublet centered at δ 1.15 on addition of D_2O, possibly a consequence of the two forms of **8** as hydroxy ketone and hemiacetal forms), 3.87, 3.91 (each br s, 2 OCH_3), and 6.59 (aromatic H).

A solution of 0.200 g of crude **8** in 0.8 ml of γ-picoline was heated at 145–150° for 6 hr in an atmosphere of nitrogen. The cooled reaction mixture was diluted with water, made acidic with dilute hydrochloric acid, and extracted with chloroform. The chloroform layer was extracted with 5% sodium bicarbonate and the alkaline extract was acidified with dilute hydrochloric acid followed by extraction with chloroform to give 0.073 g of crude **9**. Tlc analysis of crude **9** showed a major spot corresponding to authentic **9**,[3] ir ($CHCl_3$) 2.80–4.30, 5.80, 5.88, and 10.31 μ.

To a stirred solution of 0.069 g of crude **9** in 20 ml of dry benzene at 10° was added 0.058 g of trifluoroacetic anhydride in 1 ml of dry benzene. After 2.5 hr, 5% sodium hydroxide was added until the reaction mixture was basic. The layers were separated, the alkaline layer was extracted with benzene, and the combined benzene layers were washed with water, dried over anhydrous sodium sulfate, and evaporated to yield 0.031 g of gummy product. Preparative thin layer chromatography on silica gel ($CHCl_3$–acetone 95:5) followed by crystallization from ether–petroleum ether furnished 0.005 g of (±) **10**, mp 124–126°, undepressed on admixture with authentic (±) **10**.[3] The ir spectra of the product and of authentic ±**10** were identical.

Registry No.—**2**, 20797-93-7; **2a**, 20797-94-8; **3**, 20797-95-9; **3a**, 20797-96-0; **3b**, 20797-97-1; **3c**, 20797-98-2; **3d**, 20797-99-3; *cis* **5a**, 20798-00-9; *trans* **5a**, 20798-01-0; **6**, 20798-02-1; (±) **10**, 20798-09-8.

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[5] Thin layer chromatography of some fractions indicated a spot of low intensity close to that of **2** which might be due to the *cis* isomer. However, no attempts were made to isolate it.