product showed six peaks (peak no., relative retention time, percent of total, and probable identity given): 1, 1.00, 48.4, 3-ethyl-1,5-dimethylindan; 2, 1.10, 6.8, unknown; 3, 1.19, 4.0, unknown; 4, 1.31, 26.0, 1,4,6-trimethyltetralin and *x,y,z*-trimethyltetralin; 5, 2.26, 4.2, *x,y,z*-trimethylnaphthalene; 6, 2.38, 10.0, 1,4,6-trimethylnaphthalene. After dehydrogenation GC showed the following (peak no., percent of total, and probable identity given): 1, 46.3, 3-ethyl-1,5-dimethylindan; 2, 6.3, unknown; 3, 3.7, unknown; 4, 0.0, trimethyltetralins; 5, 13.5, *x,y,z*-trimethylnaphthalene; 6, 30.2, 1,4,6-trimethylnaphthalene. Distillation of the dehydrogenation product gave a first fraction that was 69.3% "3-ethyl-1,5-dimethylindan" (peak no. 1). A sample collected from the gas chromatograph gave the following NMR (CCl_4): δ 7.00 (br s, 3, Ar H), 2.58 (m, 2, C_1 H and C_3 H), 2.18 (s, 3, 5-CH_3), 1.52 (m, 2, C_2 H), 1.0–1.3 (m, 2, CH_2CH_3), 1.20 (d, 3, 1-CH_3), 0.84 (t, 3, CH_2CH_3). **1,4,4,6-Tetramethyl-1,2,3,4-tetrahydronaphthalene**[17] (from **7**). A sample collected from the gas chromatograph gave the following NMR (CCl_4): δ 6.7–7.0 (complex, 3, Ar H), 2.70 (m, 1, C_1 H), 2.20 (s, 3, 6-CH_3), 1.3–1.9 (complex, 4, C_2 H and C_3 H), 1.24 (s, 3, 4-CH_3 trans to 1-CH_3), 1.20 (d, 3, 1-CH_3), 1.18 (s, 3, 4-CH_3 cis to 1-CH_3).

Synthesis of Calamenene (9). 4-Methyl-1-pentanol was prepared from isobutylmagnesium bromide and ethylene oxide as described in the literature.[18] It was converted to 4-methyl-1-bromopentane[19] (**10**) by the sodium bromide–sulfuric acid method.[20] The Grignard reagent prepared in ether from 14.6 g (0.60 mol) of Mg and 99.8 g (0.60 mol) of **10** was treated with 80.3 g (0.60 mol) of *p*-methylacetophenone. Worked up in the usual way, the reaction mixture gave 80.7 g (61%) of 6-methyl-2-(4-methylphenyl)-2-heptanol (**8**) distilling with some decomposition in the range 99–137 °C at 3.5 torr: NMR (neat) δ 7.30 (d, 2, J = 8 Hz, C_2 and C_6 Ar H), 7.00 (d, 2, J = 8 Hz, C_3 and C_5 Ar H), 3.42 (br s, 1, OH), 2.22 (s, 3, Ar CH_3), 0.9–1.9 (complex, 7, C_3 H, C_4 H, C_5 H, and C_6 H), 1.50 (s, 3, C_1 H), 0.80 (d, 6, J = 6 Hz, C_7 H). A 62.3-g sample of this alcohol (**8**), containing some dehydration product, was heated with 5 g of P_2O_5, and 4.5 mL of water was removed by distillation. The residual mixture was refluxed for 2 h and then distilled under reduced pressure. After a 3.1-g forerun, material boiling at 130–168 °C at 22 torr was collected and redistilled to give 45.9 g (81%) of **9** distilling at 127–158 °C at 27 torr. GLC analysis revealed about 7% of an impurity with a shorter retention time, which accounts for the wide range in the boiling point. For further analytical details, see the text.

Acknowledgment. George Mitchell[5] carried out the work with alcohols **5**, **6**, and **7**. The senior author is indebted to Berta Anderes, Allen W. Gin, Pi-Chun Jen, Yen-Ping Liu, and Robert Weinberger for literature searches on indans and naphthalenes.

Registry No. **1**, 583-03-9; **2**, 73177-66-9; **3**, 73177-67-0; **4**, 4396-98-9; **5**, 4423-54-5; **6**, 73177-68-1; **7**, 73177-69-2; **8**, 73177-70-5; *cis*-**9**, 72937-55-4; *trans*-**9**, 73209-42-4; **10**, 626-88-0; butyl bromide, 109-65-9; benzaldehyde, 100-52-7; 3-methylbutyl bromide, 107-82-4; 4-methylbenzaldehyde, 104-87-0; 1-methylbutyl bromide, 107-81-3; acetophenone, 98-86-2; isobutyl bromide, 78-77-3; *p*-methylacetophenone, 122-00-9; 1-methyl-1,2,3,4-tetrahydronaphthalene, 1559-81-5; 1-methylnaphthalene picrate, 2798-40-5; 1,1,7-trimethyl-1,2,3,4-tetrahydronaphthalene, 22824-34-6; *trans*-1,3-dimethyl-1,2,3,4-tetrahydronaphthalene, 39172-86-6; *cis*-1,3-dimethyl-1,2,3,4-tetrahydronaphthalene, 39172-85-5; 1,3-dimethylnaphthalene, 575-41-7; 1,4-dimethyl-1,2,3,4-tetrahydronaphthalene, 4175-54-6; 1,4-dimethylnaphthalene, 571-58-4; 1,1,3-trimethylindan, 2613-76-5; 3-ethyl-1,5-dimethylindan, 73177-71-6; 1,4,6-trimethyltetralin, 22824-32-4; trimethyltetralin, 72843-02-8; trimethylnaphthalene, 28652-77-9; 1,4,6-trimethylnaphthalene, 2131-42-2; 1,4,4,6-tetramethyl-1,2,3,4-tetrahydronaphthalene, 1634-12-4; 4-methyl-1-pentanol, 626-89-1.

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Cyclization–Rearrangement of Alkylstyrenes. 2. Applications to the Synthesis of Some Naphthalene and Phenanthrene Derivatives

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It has been shown that alkylstyrenes, upon refluxing with phosphorus pentoxide, undergo a facile rearrangement with cyclization to produce mixtures consisting largely of derivatives of indan and 1,2,3,4-tetrahydronaphthalene.[1] Alkylstyrenes are readily available by dehydration of easily prepared benzyl alcohols. The best yields of cyclization–rearrangement products are obtained, however, if the alkylstyrene is not isolated. A mixture of dehydration products, including a benzyl ether, obtained by heating a benzyl alcohol with a small amount of phosphorus pentoxide, is refluxed with fresh phosphorus pentoxide to effect cyclization. Evidently the ether undergoes acid-catalyzed cleavage and furnishes additional alkylstyrene under these conditions.

The cyclization–rearrangement of alkylstyrenes appears to have promise as a new tool for the synthesis of certain indans, tetralins, naphthalenes, and related compounds, from readily available, relatively inexpensive starting materials. The reactions can be carried out on a large scale, and the procedures are simple. The products are usually mixtures, but they are separable in principle by use of modern chromatographic techniques.

In this paper are described short syntheses of 1,5-dimethylnaphthalene and 1-methylphenanthrene which make use of cyclization–rearrangement of an alkylstyrene as a crucial step. These compounds were chosen to test the utility of the method because they are crystalline solids and were expected to be easily separable from liquid by-products by filtration and purification by recrystallization from a solvent.

1,5-Dimethylnaphthalene was synthesized from 2-methylbenzaldehyde in 15% overall yield in accordance with Scheme I. Essentially three steps are involved, since the alkylstyrene is not isolated. The method compares favorably in ease and number of operations with previously reported syntheses of 1,5-dimethylnaphthalene.[2]

1-Methylphenanthrene was synthesized from 1-bromonaphthalene in three steps and 23% overall yield in accordance with Scheme II. The method compares favorably in ease and number of operations with Haworth's six-step synthesis from naphthalene.[3]

In a similar fashion, we have obtained 1-methylnaphthalene in 95% purity and 35% overall yield from 1-phenyl-1-pentanol and 1,4-dimethylnaphthalene in 99% purity and 11% overall yield from 2-phenyl-2-hexanol by catalytic dehydrogenation of cyclization–rearrangement products described earlier.[1] These liquid naphthalene derivatives were separated by distillation from other components of the reaction mixtures, and the yields were

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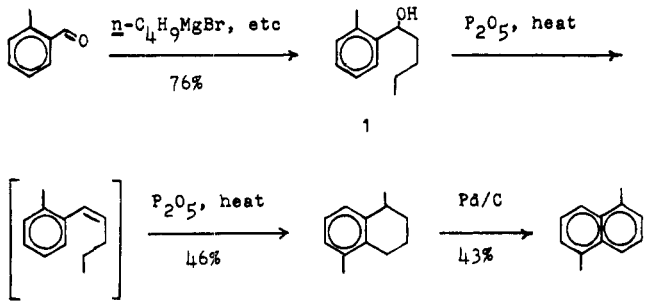
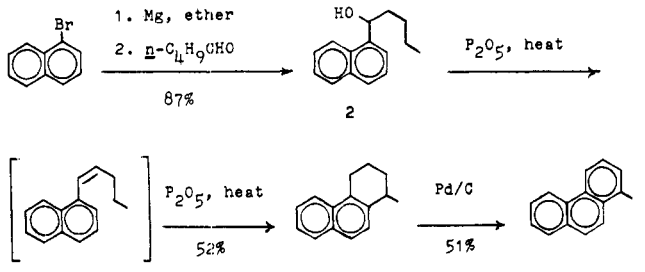
Scheme I



Scheme II



probably not as good as could be realized by use of chromatographic or chemical (picrate formation and regeneration, for example) methods of separation.

Experimental Section

1,5-Dimethylnaphthalene. The alcohol 1-(2-methylphenyl)-1-pentanol (1) was prepared in the usual way from freshly distilled 2-methylbenzaldehyde (53.6 g, 0.45 mol) and an ethereal solution of *n*-butylmagnesium bromide prepared from 14.7 g (0.60 mol) of magnesium and 95.6 g (0.698 mol) of 1-bromobutane. The yield of alcohol distilling at 119–132 °C (1.8 torr) was 60.3 g (75.5%) [lit.[4] bp 84 °C (0.6 torr)]. The alcohol 1 (56.3 g, 0.32 mol) was heated in a simple distillation apparatus with 3 g of phosphorus pentoxide until the distillation of water ceased. Some organic material that had distilled with the water was returned to the flask. The flask was fitted with an upright air-cooled reflux condenser, 2 g of fresh P_2O_5 was added, and the mixture was refluxed 2 h. It was then distilled under reduced pressure. A middle fraction, 27.2 g, distilling at 95–210 °C (23 torr), was redistilled and yielded 23.8 g (46.4% as $C_{12}H_{16}$) distilling at 119–126 °C (21 torr). Analysis by NMR spectroscopy and GLC[1] indicated a mixture containing 69.8% 1,5-dimethyl-1,2,3,4-tetrahydronaphthalene. The mixture (23.0 g) was heated with 1 g of 10% palladium on charcoal catalyst 4 h. The catalyst was removed by filtration with suction while the mixture was still hot. 1,5-Dimethylnaphthalene crystallized in the filtrate and was recrystallized from ethanol: yield 9.67 g (43.1%); mp 75 °C (lit.[2a] mp 77–78 °C).

α-Butyl-1-naphthalenemethanol[5] (2). A Grignard reagent was prepared in ether from 24.32 g (1 mol) of Mg and 217.8 g (1.05 mol) of 1-bromonaphthalene. To this was added an ethereal solution of 77.6 g (0.90 mol) of freshly distilled pentanal [bp 25–30 °C (24 torr)]. The semisolid reaction mixture was refluxed with stirring for 0.5 h. After workup in the usual way, an attempt was made to distill the product under reduced pressure. After removal of a small forerun distilling to 85 °C (5 torr), the distillate began to solidify in the side arm of the Claisen flask being used, and the attempt at distillation was abandoned. The residue in the flask solidified upon cooling and was used without further purification: yield 195.3 g; mp 56–62 °C (lit.[6] mp 65–66 °C). This crude product probably contained naphthalene and 1-bromonaphthalene as impurities.

1-Methylphenanthrene. The crude alcohol 2 (76.7 g) was heated with 7 g of phosphorus pentoxide. After removal of 4 mL of water, the mixture was boiled 2 h beneath an open air-cooled reflux condenser. It was then distilled under reduced pressure. There was obtained a middle fraction, 46.9 g, distilling at 135–180 °C (2.8 torr). After two redistillations to remove some solid, evidently P_2O_5, there was obtained 37.0 g of product distilling at 124–157 °C (1.9 torr); yield 52.6% as $C_{15}H_{16}$. Examination by GLC and NMR spectroscopy[1] indicated it was 79.5% 1-methyl-1,2,3,4-tetrahydrophenanthrene.[7] The presence of other components accounts for the wide range in the boiling point.

Of the cyclization product so obtained, 35.9 g was dehydrogenated by boiling for 2 h with 3.4 g of a 10% Pd/C catalyst with magnetic stirring. The mixture was filtered with suction while hot. The semisolid filtrate was redissolved in hot 95% ethanol and recrystallized. In a second recrystallization, Norit was used in an effort to remove some color but was not very effective. There was obtained 18.0 g (51.2%) of 1-methylphenanthrene as a golden brown microcrystalline solid, mp 118–120 °C (lit.[3] mp 118 °C).

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Registry No. 1, 73178-44-6; 2, 3042-60-2; 1,5-dimethylnaphthalene, 571-61-9; 2-methylbenzaldehyde, 529-20-4; butyl bromide, 109-65-9; 1,5-dimethyl-1,2,3,4-tetrahydronaphthalene, 21564-91-0; 1-bromonaphthalene, 90-11-9; pentanal, 110-62-3; 1-methylphenanthrene, 832-69-9; 1-methyl-1,2,3,4-tetrahydrophenanthrene, 1559-81-5.

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Conversion of L-Tyrosine to L-Phenylalanine. Preparation of L-[3',5'-$^{13}C_2$]Phenylalanine

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The importance of specifically ^{13}C-enriched amino acids, peptides, and proteins for a variety of chemical, physical, and biological studies related to structure, dynamics, metabolism, etc., has been increasingly recognized. However, at present, only a limited number of studies have been done due to the unavailability or high cost of these compounds.

In continuation of our program[1] to develop simple high yield syntheses of specifically ^{13}C-labeled amino acids and peptide hormones, we now report the preparation of L-[3',5'-$^{13}C_2$]phenylalanine.

We recently synthesized and resolved DL-[3',5'-$^{13}C_2$]-tyrosine[1b] (90% ^{13}C enriched) in a 10-step synthesis with an overall yield of 22%, using [1,3-$^{13}C_2$]acetone as the source of label. The ready availability of labeled tyrosine prompted us to attempt its conversion to [3',5'-$^{13}C_2$]-phenylalanine.

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