Assignment of Stereochemistry to 7. Reduction of 7 in ethanol with hydrogen in the presence of 10% Pd on carbon gave 1,4-dihydroxy-1,2,3,4-tetrahydronaphthalene (8), mp 138°. This material was indistinguishable by mp, nmr, and glc (as the diacetate, 3% OV-17, 170°, retained 9.5 min) from a sample prepared by catalytic reduction of 1.[14] The diol 7 (170 mg) was acetylated with acetic anhydride in pyridine and the crude product was then reduced in 8 ml of benzene with deuterium gas in the presence of 10 mg of Wilkinson's catalyst (free diol did not reduce readily). The reaction was complete in 8 days. After removal of the solvent under reduced pressure, the product was deacetylated in 80% ethanol-water containing an excess of sodium hydroxide. The ethanol was removed, water was added, and the pH was adjusted to 7 with acetic acid. Extraction with ethyl acetate provided 8-*cis*-2,3-d_2; incorporation of two atoms of deuterium was confirmed by its mass spectrum.

Saturated $CDCl_3$ solutions (400 μl) of deuterated and normal 8 at 20° were used to determine their nmr spectra in the presence of 3 mg of Eu(fod)$_3$. Normal 8 showed the four protons at the 2 and 3 positions to be split into two separate groups at δ 2.66 and 3.16, presumably due to hydrogens cis and trans to the hydroxyl groups. The benzylic protons moved to δ 6.0 and the aromatic protons split into two groups at δ 7.5–7.6 and 8.1–8.3. The corresponding spectrum of deuterated 8 lacked the absorption at δ 2.66, and when the benzylic protons were irradiated, the signal at δ 3.16 sharpened considerably. This observation confirms the assignment of the chemical shifts in the complex and, together with the cis addition of deuterium, is consistent with the hydroxyl groups in 8 as cis.

Dehydration of the Dihydrodiols 5 and 7. Rates were measured by following the decrease in absorption at 265 nm and the increase at 295 nm for 5 and 7, respectively, in dioxane–water (1:1) which was 0.6 *M* in HCl. The rates at 25° for 5 and 7 are 5.4×10^{-4} and 2.8×10^{-2} sec^{-1}, respectively. Only α-naphthol could be detected by tlc as a product from 7.

Acknowledgment. The authors are very indebted to Dr. P. A. Argabright of the Denver Research Center, Marathon Oil Co., Littleton, Colo., for a sample of 8 prepared by the catalytic reduction of 1. We thank Dr. P. Roller of the National Cancer Institute for obtaining the accurate mass measurement reported.

Registry No.—1, 130-15-4; 3, 25129-70-8; 5, 31966-70-8; 6, 50987-67-2; 7, 51096-10-7; 8, 50987-68-3.

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Formation of a Cyclohexane Ring by Condensation of a Nitro Ketone and an Aldehyde[1a]

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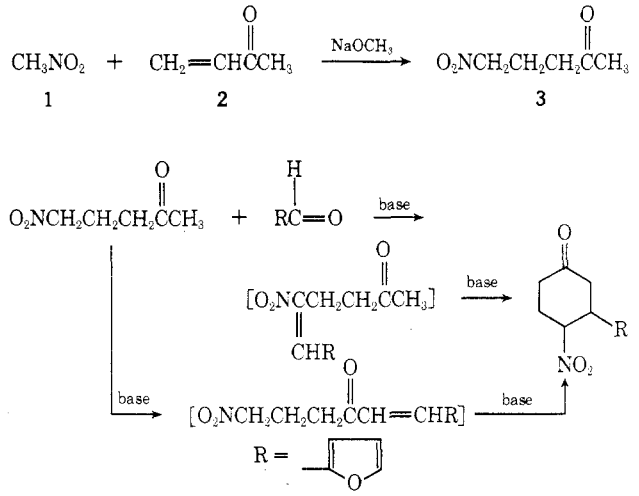
Received November 2, 1973

5-Nitro-2-pentanone (3) and furfural were used to study the feasibility of using a condensation reaction to form a cyclohexane ring. The Schiff base of furfural was condensed with the ethylene ketal of 5-nitro-2-pentanone in acetic acid to give 1-(2-furyl)-2-nitro-1-hexen-5-one 5-ethylene ketal (11). The ketal was removed and an intramolecular Michael reaction was effected using an enamine to form 3-(2-furyl)-4-nitrocyclohexanone (21). Practical syntheses of 1-methoxy-5-nitro-2-pentanone (22) and *trans*-2,6-dimethyl-2-heptenal (23) have been developed.

Earlier papers have reported experiments on the preparation and Birch reduction of 2,3-dihydrobenzofurans as possible intermediates for syntheses in the fumagillin series.[2] Corey has recently reported a synthesis of fumagillin, using a Diels–Alder reaction to form the carbocyclic ring.[3]

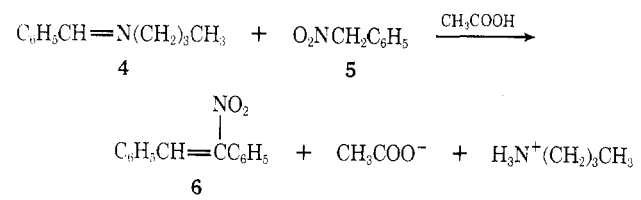
We considered that the cyclohexane ring of fumagillin could be formed by the condensation of a γ-nitro ketone with an aldehyde, which would allow a stereoselective synthesis. To test the feasibility of such a reaction, the condensation of furfural with 5-nitro-2-pentanone (3) was studied; these compounds are accessible and are reasonable models for the proposed syntheses.

5-Nitro-2-pentanone (3) was obtained by a modification of the published procedure.[4] An attempt to cyclize 3 with furfural according to the following scheme gave only tars, probably owing to the high reactivity of α,β-unsaturated nitro compounds.[5] A two-step condensation was therefore



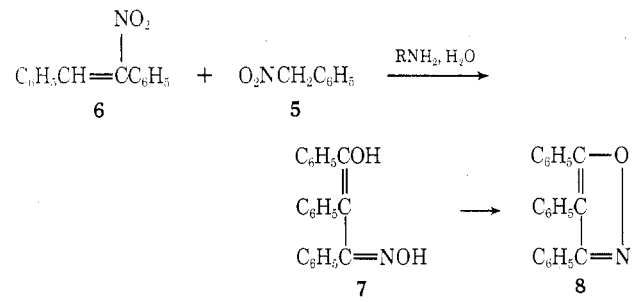
examined; the ethylene ketal of **3** was used, because this has only one active site for condensation. A mild method for the formation of the nitro olefin was then sought.

Robertson has reported a method of making α-nitrostilbene (**6**) by using the Schiff base of an aromatic aldehyde (**4**) with the nitro compound (**5**) in acetic acid.[6]



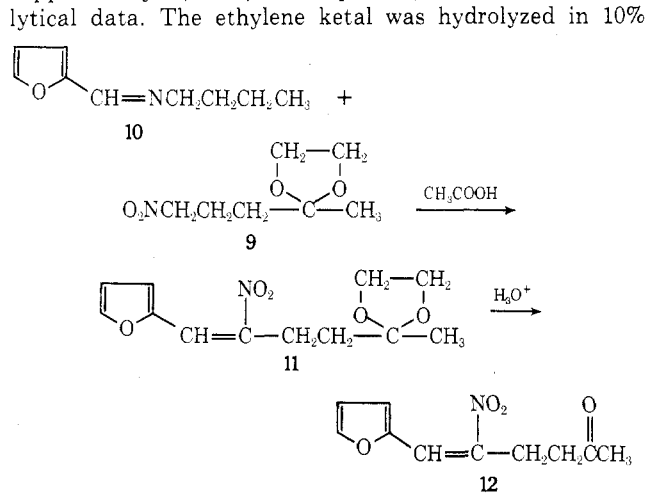
A kinetic study of the Knoevenagel reaction between nitromethane and piperonal, using *n*-butylamine as catalyst, indicated that the Schiff base was the intermediate.[7] It was found that the Schiff base reacted rapidly with nitromethane when catalyzed by *n*-butylammonium acetate, whereas piperonal did not react with nitromethane using the same catalyst.

Worrall found that an α-nitrostilbene will react with another molecule of the nitro alkane to form **7** and **8**.[8] A



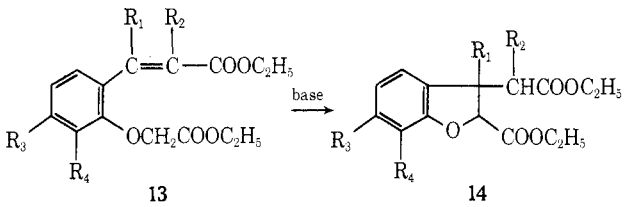
trace of water was necessary for formation of these products. Robertson reasoned that, to eliminate these side products, the water could be removed by forming the Schiff base before reacting with the nitro alkane; then acetic acid was added to remove the amine which is formed when the α-nitrostilbenes were formed.

This method was applied to the ethylene ketal of 5-nitro-2-pentanone (**9**) by treating with the Schiff base of furfural and *n*-butylamine (**10**) in acetic acid at room temperature for 40 hr; this gave a 72% yield of compound **11** in crystalline form, mp 93–95°. The structure **11** was supported by ir, nmr, mass spectral, and elemental analytical data. The ethylene ketal was hydrolyzed in 10%



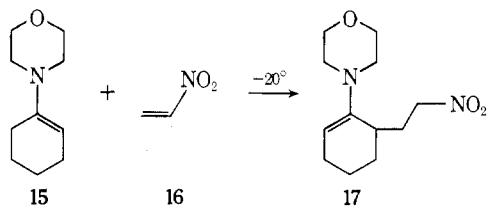
HCl solution to give 1-(2-furyl)-2-nitro-1-hexen-5-one (**12**) in 85% yield, mp 63.5–64.5°; the compound was characterized as above.

The next step was an internal Michael reaction involving the α,β-unsaturated nitro group of the molecule as acceptor and the methyl ketone part as donor. Nitro compounds effectively activate a double bond for such an addition and there are a number of examples of such Michael additions in the literature.[9] An internal Michael reaction has been reported by Koelsch on compounds such as **13** to form compounds of the structure **14**.[10] He found that this cyclization was not subject to the inhibiting effect by substituents on the α- and β-carbon atoms as are intermolecular Michael reactions. The yields obtained indicated that the reaction was essentially complete, with no unfavorable equilibrium apparent.



A variety of conditions was tried to effect the cyclization of **12**. Conditions which were strong enough to abstract the proton from the $CH_3C{=}O$ ($pK_a \cong 20$)[11] resulted in tars, probably owing to the high reactivity of the nitro olefin. A method was then needed which would produce a good nucleophilic center at the methyl carbon and also be mild enough to prevent polymerization of the nitro olefin. An enamine intermediate seemed to fit these qualifications. Enamines have been reported to be efficient nucleophiles in the Michael reaction.[12]

Kuehne and Foley have reported the Michael addition of the enamine **15** to nitroethylene (**16**) to give the product **17** in 80% yield.[13] The weak base morpholine was used



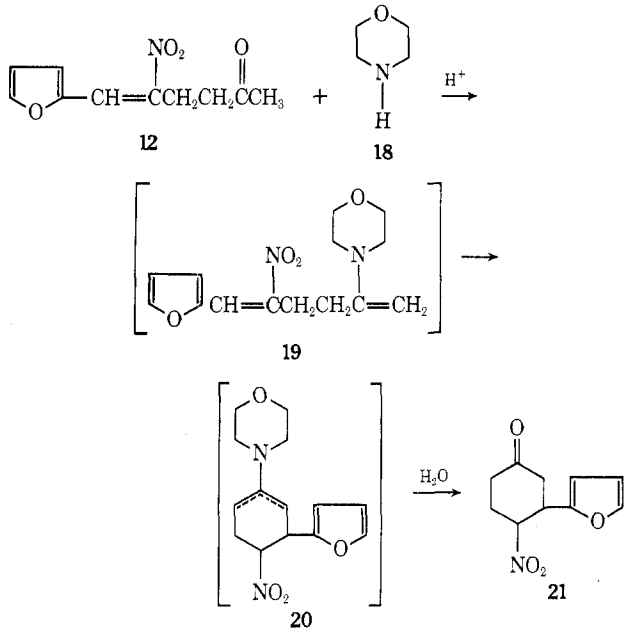
because it was unlikely to cause polymerization of nitroethylene.

Application of Stork's conditions[14] with morpholine to **12** caused the disappearance of the starting ketone and appearance of a peak which was probably the enamine, as shown by vpc analysis. The enamine was then hydrolyzed by refluxing with water and benzene overnight. After work-up, an oil resulted which was purified by column chromatography on silica gel. A crystalline substance (**21**) resulted in 30–40% yield, mp 76–77.5°. The reaction is thought to go through the route shown.

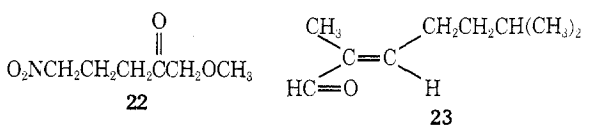
The enamine **19** is formed, which quickly cyclizes under the reaction conditions to the enamine **20**; this is then hydrolyzed to give the product **21**.

The infrared spectrum for 3-(2-furyl)-4-nitrocyclohexanone (**21**) showed absorptions of 1710 cm^{-1} for the carbonyl and 1540 cm^{-1} for the C–NO_2 stretch. The nmr spectrum was consistent with the assigned structure (see Experimental Section). A satisfactory elemental analysis was obtained and the mass spectrum yielded a molecular ion at *m/e* 209. A decoupling experiment showed that the coupling constant for the protons in the 3 and 4 positions of **21** is 8.5 Hz, which is in good agreement with that expected for a trans diaxial configuration for these two protons.[15] This configuration was expected since the diequatorial configuration of the two substituents should be the more stable.

To prepare compounds in the fumagillin series,[16] by the general scheme leading to **21**, 1-methoxy-5-nitro-2-penta-

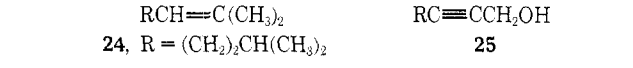


none (22) and *trans*-2,6-dimethyl-2-heptenal (23, aldehyde group trans to the alkyl groups) would be suitable components. Although the condensation of 22 and 23 was not carried out, both 22 and 23 were synthesized by practical methods, and the procedures will be described briefly, because they represent a considerable amount of experimentation, in which numerous approaches were examined.



Compound 22 was prepared in 50% yield by the addition of nitromethane (in large excess) to methoxymethyl vinyl ketone,[17] with Triton B as base.[18] Numerous attempts to generate the vinyl ketone *in situ* from various precursors, and to add nitromethane in one step, were unsuccessful.[19] The use of other bases[4] for catalyzing the addition of nitromethane to the vinyl ketone was unsatisfactory.

The unsaturated aldehyde 23 was made by oxidizing the unsaturated hydrocarbon 24 (prepared by a Wittig reaction) by selenium dioxide; the reaction is stereospecific.[20]



The procedure of Corey[21] for reduction, iodination, and methylation of propargylic alcohols was unsatisfactory, giving a mixture of the 2- and 3-iodoallylic alcohols. Another procedure,[21] designed to yield the carboxylic acid corresponding to 23, gave a mixture of cis and trans isomers, separated only with difficulty.

Experimental Section[22]

5-Nitro-2-pentanone (3). 5-Nitro-2-pentanone was made as described except that a 1-hr reflux was used instead of a 10-hr reflux.[4] Starting with 160 g of nitromethane and 25 g of methyl vinyl ketone, a yield of 22.3 g (48%) of the desired product was obtained, bp 76° (0.25 mm) [lit. bp 85° (0.1 mm)].[4] The nmr spectrum gave peaks at δ 2.13 (s, 3 H, O=CCH$_3$), 2.1–2.8 (m, 4 H, CH$_2$CH$_2$C=O), and 4.41 (t, 2 H, O$_2$NCH$_2$).

The ethylene ketal of 5-nitro-2-pentanone (9) was prepared by refluxing 22.3 g of the nitro ketone with 30 ml of ethylene glycol, 100 ml of benzene, and a trace of *p*-toluenesulfonic acid for 19 hr with a water separator; the benzene solution was washed several times with a saturated solution of sodium bicarbonate and then with water. The combined water solutions were washed with chloroform and this was added to the benzene solution. The combined organic solution was dried over magnesium sulfate and the solvent was removed under reduced pressure. The ketal was used without further purification. The nmr and ir spectra were consistent with the structure of this compound.

Schiff Base of Furfural (10). To a 250-ml round-bottom flask were added 25 g (0.26 mol) of freshly distilled furfural, 19 g (0.26 mol) of *n*-butylamine, and 100 ml of benzene. The flask was fitted with a water separator and allowed to reflux until the proper amount of water had been collected (about 3 hr). The solvent was then removed under reduced pressure and the Schiff base was used without any further purification. The nmr and ir spectra were consistent with the structure of this compound.

1-(2-Furyl)-2-nitro-1-hexen-5-one 5-Ethylene Ketal (11). A procedure similar to that of Robertson was used.[6] To a solution of the ketal of 5-nitro-2-pentanone made above in 30 ml of glacial acetic acid was added 28.3 g of the Schiff base. The flask was purged with nitrogen and the solution was allowed to stir at room temperature under a nitrogen atmosphere. After 40 hr, the crystals in the solution were separated by suction filtration and washed with cold ethanol. More crystals were obtained by pouring the filtrate over cracked ice, separating the crystals, and washing with cold ethanol. The total yield was 31.2 g (72%) of yellow crystals, mp 93–95° (from ethanol). The absorptions in the nmr spectrum are δ 1.40 (s, 3 H, CH$_3$), 1.94 (m, 2 H, CH$_2$), 3.14 (m, 2 H, CH$_2$C=C), 3.99 (s, 4 H, OCH$_2$CH$_2$O), 6.60 (q, 1 H, 4-furan proton), 6.94 (d, 1 H, 3-furan proton), 7.65 (d, 1 H, 5-furan proton), and 7.82 (s, 1 H, CH=C). An ir spectrum gave peaks at 2980 and 2880 (C–H stretch), 1650 (C=C stretch), and 1510 cm^{-1} (nitro). A mass spectrum gave a molecular ion at *m/e* 253.

Anal. Calcd for C$_{12}$H$_{15}$NO$_5$: C, 56.91; H, 5.97. Found: C, 56.70; H, 6.11.

1-(2-Furyl)-2-nitro-1-hexen-5-one (12). The ethylene ketal of 1-(2-furyl)-2-nitro-1-hexen-5-one (11, 28.9 g) was refluxed for 1 hr with 100 ml of 10% HCl and 100 ml of benzene. A conventional work-up gave, after removal of solvent, 20.8 g (84%) of yellow needles, mp 63.5–64.5°. The absorptions of the nmr spectrum are δ 2.12 (s, 3 H, CH$_3$), 2.65 (m, 2 H, CH$_2$C=O), 3.18 (m, 2 H, CH$_2$C=C), 6.50 (q, 1 H, 4-furan proton), 6.80 (d, 1 H, 3-furan proton), 7.56 (d, 1 H, 5-furan proton), and 7.71 (s, 1 H, CH=C). The ir spectrum gave peaks at 1700 (carbonyl) and 1510 cm^{-1} (nitro).

Anal. Calcd for C$_{10}$H$_{11}$NO$_4$: C, 57.41; H, 5.30. Found: C, 57.50; H, 5.30.

3-(2-Furyl)-4-nitrocyclohexanone (21). A 250-ml three-neck round-bottom flask was equipped with a water separator with condenser and a nitrogen inlet tube. The system was purged with nitrogen and the reaction was run under a nitrogen atmosphere. To the flask were added 5 g (0.024 mol) of 1-(2-furyl)-2-nitro-1-hexen-5-one (12), 65 ml of benzene, 3.1 g (0.036 mol) of morpholine, and a catalytic amount of *p*-toluenesulfonic acid. The solution was refluxed for 20 hr. The enamine was hydrolyzed by adding 50 ml of water to the solution and refluxing overnight. The benzene solution was separated from the water and the water layer was extracted with ether. The ether solution was added to the benzene solution and the combined organic solution was washed with 5% HCl solution, saturated sodium bicarbonate solution, and water. The combined water washings were extracted once with ether and this was added to the organic solution. This solution was then dried over magnesium sulfate and the solvent was removed under reduced pressure, yielding a dark oil.

The oil was purified by chromatography on silica gel (activity grade 1). The solvent used at the start was a 50:50 benzene–hexane mixture. The first fractions collected contained the remainder of the starting ketone. The fractions became less colored and the solvent was gradually changed to 100% benzene. The column itself became quite dark, while the liquid remained a very pale yellow. The solvent was removed under reduced pressure, yielding 2.1 g of crude product. This was further purified by sublimation at 70° (0.05 mm) to yield 1.6 g (32%) of white crystals, mp 76–77.5°. The absorptions of the nmr spectrum are δ 2.54 (m, 4 H, CH$_2$CH$_2$), 2.76 (d, 2 H, CH$_2$C=O), 4.00 (q, 1 H, CHCHNO$_2$), 5.11 (m, 1 H, CHNO$_2$), 6.29 (d, 1 H, 3-furan proton), 6.32 (m, 1 H, 4-furan proton), and 7.39 (m, 1 H, 5-furan proton). The ir spectrum showed peaks at 1710 (carbonyl) and 1540 cm^{-1} (nitro). The mass spectrum gave a molecular ion at *m/e* 209.

Anal. Calcd for C$_{10}$H$_{11}$NO$_3$: C, 57.41; H, 5.30. Found: C, 57.22; H, 5.67.

Methoxymethyl Vinyl Ketone.[17] 1,4-Dimethoxy-2-butanone[23] (10.0 g) was heated and stirred with 12.5 g of sodium benzoate plus a small amount of hydroquinone in a flask fitted with a dis-

tillation head and condenser. The temperature in the distillation head rose to 130° at the end of the distillation. The liquid collected weighed 6.0 g. This was a mixture of methanol, water, and a small amount of starting material, and the desired methoxymethyl vinyl ketone was estimated by nmr to be 2.9–3.0 g. Peaks in the nmr spectrum (crude mixture) for methoxymethyl vinyl ketone are δ 3.36 (s, 3 H, $-OCH_3$), 4.26 (s, 2 H, $-CH_2O-$), 5.86 (d of d, 1 H, C=CH), and 6.38 (m, 2 H, CH_2=C). The liquid was dried over magnesium sulfate for use in the reaction with nitromethane.

1-Methoxy-5-nitro-2-pentanone (22). To a 1-l. round-bottom three-neck flask, fitted with an addition funnel, condenser, and nitrogen inlet, were added 480 g (~100 equiv) of nitromethane, 150 ml of ether, and 8 ml of 40% Triton B in methanol.[18] This was heated to reflux, and a solution containing approximately 7.9 g of methoxymethyl vinyl ketone in ether was added dropwise. The resulting mixture was allowed to reflux for 20 hr. The solution was cooled, the solvent was removed under reduced pressure, and the residue was taken up in chloroform, and this solution was washed with 5% HCl solution, 10% sodium bicarbonate, and water. The solution was dried over magnesium sulfate and the solvent was removed under reduced pressure. The residue was distilled, yielding 6.3 g (50%) of a pale yellow liquid, bp 86–89° (0.05 mm). An ir spectrum (liquid film) showed peaks at 1720 (carbonyl) and 1540 cm^{-1} (nitro). The mass spectrum gave a molecular ion at *m/e* 161. The nmr spectrum was in agreement with structure **22**. An elemental analysis was performed on the semicarbazone, mp 145–146° (from water).

Anal. Calcd for $C_7H_{14}N_4O_4$: C, 38.53; H, 6.47. Found: C, 38.67; H, 6.54.

4-Methylpentanal was prepared in 35% overall yield by the reaction of isoamylmagnesium bromide on ethyl orthoformate, followed by hydrolysis of the acetal, and isolation of the aldehyde as the bisulfite product;[24] the free aldehyde had bp 120–122° (reported[25] bp 124°).

2,6-Dimethyl-2-heptene (24). A three-neck 250-ml round-bottom flask was fitted with a mechanical stirrer, rubber septum, and condenser with nitrogen inlet. The system was purged with nitrogen and a nitrogen atmosphere was maintained throughout the reaction. To the flask was added 43.2 g (0.1 mol) of isopropyltriphenylphosphonium iodide[26] in 100 ml of ether. The suspension was cooled in an ice bath and 0.11 mol of *n*-butyllithium was added by means of a syringe through the rubber septum. The solution was allowed to warm to room temperature and was then stirred at this temperature for 3 hr. The rubber septum was replaced with a dropping funnel and 10 g (0.1 mol) of 4-methylpentanal in 20 ml of ether was added dropwise. This was allowed to stir at room temperature for 48 hr. During this time the triphenylphosphine oxide precipitated out of the solution. The liquid was then separated from the solid by filtration and the solid was washed several times with petroleum ether (bp 30–60°). The solvent was removed from the solution under reduced pressure. The product was distilled to yield 5.2 g (41%), bp 135–136° (lit. bp 142–143°).[27] The nmr spectrum (neat) showed absorptions at δ 0.90 (d, 6 H, CH_3CHCH_3), 1.13–1.54 (m, 3 H, CH_2CH), 1.61 (s, 3 H, methyl trans to alkyl), 1.68 (s, 3 H, methyl cis to alkyl), 2.04 (q, 2 H, C=CCH_2), and 5.25 (m, 1 H, C=CH).

trans-**2,6-Dimethyl-2-heptenal (23).** A procedure similar to that of Bhalerao and Rapoport[20] was used. To a 100-ml round-bottom flask were added 5.2 g (0.041 mol) of 2,6-dimethyl-2-heptene, 9.6 g (0.044 mol) of selenium dioxide, and 70 ml of ethanol. The mixture was allowed to reflux for 15 hr. The solvent was removed under reduced pressure and the residue was dissolved in ether. This was then washed with a saturated sodium bicarbonate solution and dried over magnesium sulfate, and the solvent was removed under reduced pressure. The product was distilled to give 2.0 g (35%), bp 82–85° (10 mm). The ir spectrum (CCl_4) showed peaks at 2940 (C–H stretch), 1670 (carbonyl), and 1400 cm^{-1} (C–H bend). The mass spectrum gave a molecular ion at *m/e* 140.

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.39; H, 11.41.

The nmr showed absorptions at δ 0.92 [d, 6 H, $(CH_3)_2CH$], 0.95–1.6 [m, 3 H, $(CH_3)_2CHCH_2$], 1.69 [s, 3 H, C=$C(CH_3)$], 2.32 (q, 2 H, CH_2C=C), 6.31 (m, 1 H, HC=C), and 9.20 (s, 1 H, CHO).

Registry No.—3, 22020-87-7; **9,** 19639-74-8; **10,** 51004-05-8; **11,** 51004-06-9; **12,** 51004-07-0; **21,** 51004-08-1; **22,** 51004-09-2; **22** semicarbazone, 51021-62-6; **23,** 51004-04-7; **24,** 5557-98-2; furfural, 98-01-1; *n*-butylamine, 109-73-9; methoxymethyl vinyl ketone, 43042-58-6; 1,4-dimethoxy-2-butanone, 25680-86-8; 4-methylpentanal, 1119-16-0; isoamyl bromide, 107-82-4; ethyl orthoformate, 122-51-0; isopropyltriphenylphosphonium iodide, 24470-78-8.

References and Notes

(1) (a) Aided by Grant AI-08424 from the National Institutes of Health. (b) National Science Foundation Trainee, 1970–1971; Du Pont Fellow, 1972–1973.
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