(about 10 mg) was heated to 85–90° and treated over 5 min with bromine (1.31 g). Direct crystallization of the product from benzene gave 610 mg. Several recrystallizations from benzene–cyclohexane followed by sublimation gave an analytical sample: mp 79–81°; ir 1823 (m), 1780 (s), 1024 (s) cm^{-1}; nmr δ 4.72 (t, J = 8 Hz, 1 H), 2.38 (d, J = 8 Hz, 2 H), 1.47 (s, 3 H), 1.43 (s, 3 H).

Anal. Calcd for $C_7H_9O_3Br$: C, 38.03; H, 4.10; Br, 36.15. Found: C, 37.97; H, 4.12; Br, 35.89.

2,2-Dimethyl-4-hydroxyglutaric Acid Lactone (8). A. Authentic Sample.—A mixture of bromo anhydride **7** (150 mg) and 10 ml of 5% aqueous sodium hydroxide was heated at reflux under nitrogen for 3 hr. The resulting clear solution was taken to dryness *in vacuo;* the residue was taken up in hydrochloric acid, and the solution was again taken to dryness. Extraction of the residue with several portions of hot benzene gave 89 mg (90%) of crude product. Several recrystallizations from benzene–cyclohexane gave an analytical sample: mp 82–84°; ir (KBr disk) 3600–2800 (broad), 1780 (s), 1750 (s), 1178 (s), 1165 (s), 1060 (s) cm^{-1}; nmr ($CDCl_3$) δ 10.71 (s, 1 H), 4.95 (t, J = 8 Hz, 1 H), 2.42 (dd, J_1 = 6 Hz, J_2 = 8 Hz, 2 H), 1.31 (s, 6 H).

Anal. Calcd for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found: C, 53.16; H, 6.35.

B. By Saponification of 5.—A solution of lactone methyl ester **5** (300 mg) in 40 ml of methanol containing 6.9 ml of 0.5 *M* sodium hydroxide was kept overnight at room temperature under nitrogen and was then taken to dryness. The residue was taken up in water, acidified with concentrated HCl to pH 2, taken again to dryness, and then worked up as in A above. There was recovered 260 mg (94%) of crude crystalline product. Two recrystallizations gave a sample with melting point, mixture melting point, ir, and nmr spectra identical with those of an authentic sample.

2,2-Dimethyl-4-hydroxyglutaric Acid Lactone Methyl Ester (5). A. Authentic Sample.—A solution of lactone carboxylic acid **8** (50 mg) in 10 ml of ether was treated with excess ethereal diazomethane and allowed to remain at room temperature for 2 hr. The solution was taken to dryness and the product twice crystallized from benzene–cyclohexane: mp 49.5–50°; ir (KBr disk) 2950 (m), 1775 (s), 1760 (s), 1220 (ms), 1195 (ms), 1065 (s) cm^{-1}; (CCl_4) 2950 (m), 1800 (s), 1775 (ms), 1750 (ms), 1200 (ms), 1110 (m), 1070 (m) cm^{-1}; nmr δ 4.80 (t, J = 7.5 Hz, 1 H), 3.80 (s, 3 H), 2.29 (dd, J_1 = 7.5 Hz, J_2 = 6.5 Hz, 2 H), 1.25 (s, 6 H).

B. From Bromination of Amino Ester 2a.—Distillation of the crude bromination product described above gave a fraction of variable amount, bp 85–88° (0.3 mm), which spontaneously crystallized in the cold. Recrystallization of this material first from CCl_4 and then from benzene–cyclohexane gave stout needles, melting point, mixture melting point, and ir and nmr spectra identical with those of an authentic sample.

Anal. Calcd for $C_8H_{12}O_4$: C, 55.80; H, 7.03. Found: C, 55.97; H, 7.25.

Registry No.—**1**, 1192-14-9; **2b**, 20104-44-3; **3a**, 20104-45-4; **3b**, 20104-46-5; **4b**, 20104-47-6; **5**, 20104-48-7; **7**, 20104-49-8; **8**, 20104-52-3; **10**, 20104-53-4.

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Condensation of *p*-Nitrotoluene with Aldehydes

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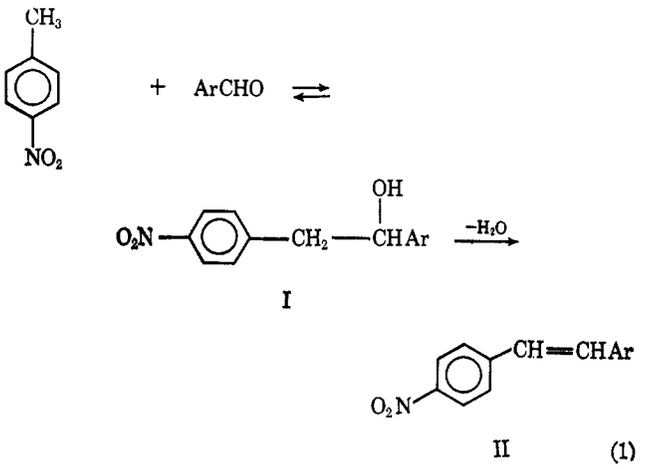
Base-catalyzed condensation reactions of *p*-nitrotoluene are complicated by the facile oxidation[1,2] and dimerization[2,3] of the *p*-nitrotoluene carbanion. Condensation with aldehydes has resulted in very poor yields of the desired stilbenes[4] (eq 1), and has led to the use of the condensation–decarboxylation sequence employing *p*-nitrophenylacetic acid[5] (eq 2).



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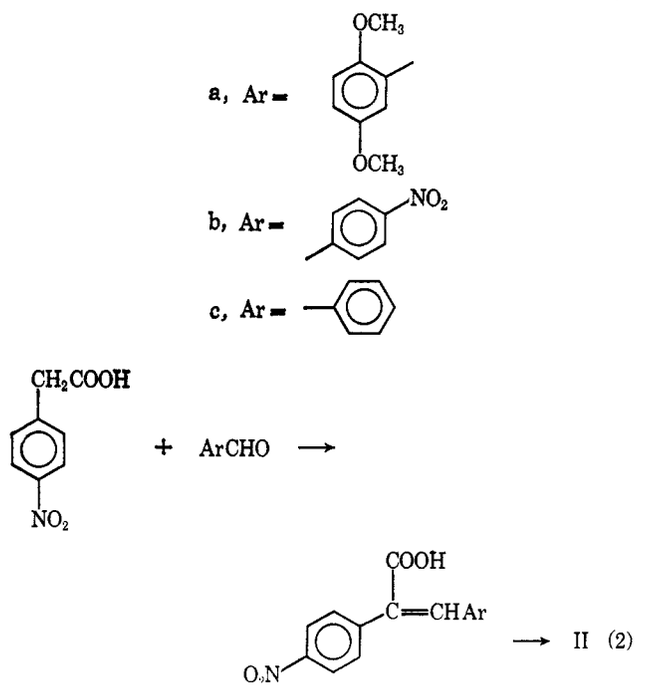

(2)

Despite the unpromising past performance of the *p*-nitrotoluene carbanion in condensation reactions,[3,4] it was expected that the proper choice of solvent might improve the situation. That highly polar aprotic solvents can greatly assist a variety of anionic processes has been abundantly demonstrated in recent years.[2,6] Therefore, the condensation of *p*-nitrotoluene with aromatic aldehydes in dipolar aprotic solvent systems was investigated.

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Results and Discussion

The reaction of *p*-nitrotoluene with 2,5-dimethoxybenzaldehyde was examined in a number of solvents, with several bases as catalysts and under a variety of conditions. Certain limitations were apparent at the outset. Dimethyl sulfoxide (DMSO), for example, added to the aldehyde under the reaction conditions,[6,7] to the exclusion of the desired condensation. Bases such as potassium *t*-butoxide promoted formation of 2,5-dimethoxybenzoic acid, rather than the condensation products. Of the bases (morpholine, piperidine, alkali metal hydroxides and alkoxides, tetra-*n*-butylammonium hydroxide) and solvents [DMSO, dimethylformamide (DMF), hexamethylphosphoramide] employed, a DMF–lithium hydroxide system offered the first spectral and tlc evidence of the desired stilbene reaction product, and showed that the condensation could compete favorably with the dimerization–oxidation reactions.

We sought, in subsequent experiments, to improve the yield of stilbene by increasing the severity of the reaction conditions (80–100°, 4–18 hr), by using benzene to aid in water removal, and by increasing the catalyst concentration (0.5–1.2 moles). Despite these efforts, starting material persisted at the termination of the reaction, and the products were accompanied by the usual tarry intractable matter. We were able, however, to isolate from these reaction mixtures a solid product which was shown to be the diarylethanol, Ia. Nearly quantitative yields of Ia could be obtained in 2 hr at 20–28° with a threefold excess of *p*-nitrotoluene.

Although the equilibrium nature of the reaction seemed probable from the experimental results, we sought spectral verification of this and the proposed *p*-nitrotoluene carbanion intermediate. Miller and Pobiner[8] have examined the ultraviolet and visible spectra of *p*-nitrotoluene in potassium *t*-butoxide–*t*-butyl alcohol solution and have observed bands at 362 mμ (*p*-nitrotoluene carbanion) and 557 mμ (charge-transfer complex). Neither is associated with free-radical formation. In sodium hydroxide–DMF we find an absorption at 580 mμ for *p*-nitrotoluene alone, and for the reaction mixture with dimethoxybenzaldehyde present. Most convincingly, a solution of Ia in DMF which is essentially transparent in the visible, develops a strong blue-green color and an absorption at 580 mμ on treatment with sodium hydroxide. On acidification, this solution yields recovered Ia plus *p*-nitrotoluene and dimethoxybenzaldehyde.[9]

To complete the stilbene synthesis, it remained to demonstrate that Ia was readily dehydrated to IIa. This could be accomplished with phosphoric acid, or, most conveniently, by refluxing a solution of Ia in dimethyl sulfoxide.[10] In 3 hr, there was obtained a 96.5% yield of exclusively *trans*-2,5-dimethoxy-4′-nitrostilbene (IIa).[11]

The product was of exceptional purity as evidenced by its infrared, ultraviolet, and nmr spectral data, melting point, and thin layer chromatography and was free of the minor impurities encountered in the mineral acid catalyzed dehydration. The over-all yield of 90% based on starting aldehyde represents a considerable improvement over the *p*-nitrophenylacetic acid method.[5]

p-Nitrobenzaldehyde and benzaldehyde have been condensed with *p*-nitrotoluene and the corresponding diarylethanols (Ib and Ic) prepared. This method provides a simple procedure for the synthesis of 4-nitrostilbenes and their derivatives. Of course, the equilibrium concentration, and hence the yield, of I will vary with the substrate, but the reaction appears suitable enough for general applicability.

Experimental Section[12]

***p*-Nitrotoluene Condensation. Synthesis of 1-(2,5-Dimethoxyphenyl-2-(4′-nitrophenyl)ethanol (Ia).**—To a well-stirred solution of 6.85 g (0.05 mole) of *p*-nitrotoluene and 8.3 g (0.05 mole) of 2,5-dimethoxybenzaldehyde in 100 ml of dimethylformamide was added, under nitrogen, 0.2 g (0.005 mole) of freshly ground sodium hydroxide. The reaction mixture turned bright green in 25 min at room temperature. After 2 hr, the reaction mixture was acidified with 60 ml of 5% hydrochloric acid and extracted with benzene. The benzene solution was dried and the benzene evaporated to an orange oil. Crystallization from benzene–cyclohexane (1:3) gave 8.34 g (0.027 mole, 55%) of a yellow solid, Ia, mp 99–101°. Repeated recrystallization from ethyl acetate–petroleum ether raised the melting point to 102.5–104.5°: nmr (DMSO-d_6), δ 8.09 (d, 2, Ar-**H**), 7.48 (d, 2, Ar-**H**), 6.9 (m, 3, Ar-**H**), 5.18 (m, 2, ArC**H**OH), 3.78–3.72 (2 s, 6, OCH_3), 3.0 (m, 2, CH_2).

Anal. Calcd for $C_{16}H_{17}O_5N$: C, 63.36; H, 5.65; N, 4.62. Found: C, 63.46; H, 5.82; N, 4.67.

Excess *p*-Nitrotoluene.—In a similar manner were reacted 61.6 g (0.45 mole) of *p*-nitrotoluene and 19.1 g (0.15 mole) of 2,5-dimethoxybenzaldehyde in 100 ml of dimethylformamide with 0.2 g (0.005 mole) of sodium hydroxide. The mixture turned dark green in 7 min. After 2 hr the reaction mixture was acidified with 1 ml of concentratedhydrochloric acid, filtered, and vacuum distilled. The solvent was removed at 45–52° (10 mm) and excess *p*-nitrotoluene at 90° (0.25 mm) to yield 45.15 g (0.149 mole, 99%) of a red oil which solidified on standing to a yellow solid, mp 99–101°.

The yield and quality of the product were not affected by introducing the catalyst as a 50% aqueous solution. However, as little as 3% water in the solvent gave a slower reaction rate and lower yield (75%) of inferior quality product.

In similar fashion 1,2-di(4-nitrophenyl)ethanol was prepared (Ib), mp 183–185°, in 16% yield, and 1-(4-nitrophenyl)-2-phenylethanol (Ic), mp 90–91°, in 33% yield.

Anal. Calcd for $C_{14}H_{13}NO_3$ (Ic): C, 69.12; H, 5.39; N, 5.76. Found: C, 68.93; H, 5.17; N, 5.92.

2,5-Dimethoxy-4′-nitrostilbene (IIa).—A solution of 1-(2,5-dimethoxyphenyl)-2-(4′-nitrophenyl)ethanol (Ia) (6.07 g, 0.02 mole) in dimethyl sulfoxide (40 ml) was refluxed with stirring for 3 hr. The reaction mixture was evaporated to a red oil (5.46 g) which began to crystallize at room temperature. After washing with petroleum ether, bright yellow 2,5-dimethoxy-4′-nitrostilbene (IIa) (5.50 g, 96.5%), mp 116.5–118°, was obtained. On recrystallization from cyclohexane, it had mp 119–119.5°,[13] λ_{max}^{380} (ε 19,150);[5] thin layer chromatography on a phosphor plate showed a single spot both under visible and ultraviolet light.

Registry No.—*p*-Nitrotoluene, 99-99-0; Ia, 20273-72-7; Ib, 20273-73-8; Ic, 20273-74-9.

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The Steric Course of a Ketimine Reduction

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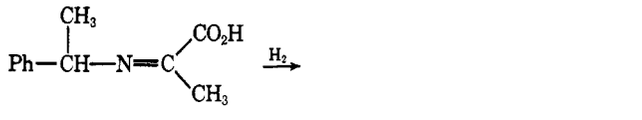
Asymmetric induction occurs when a new chiral center is formed by a reaction in which its symmetry is influenced by a second chiral center, already present in the reacting molecule. The phenomenon is most readily observed with optically active materials when the extent of asymmetric induction is evident from the optical activity of the products. For example, $R(-)$-alanine is formed in excess over the $S(+)$ enantiomer when pyruvic acid is reductively aminated with $R(+)$-α-methylbenzylamine.[2] More recently, an explanation of the stereochemistry involved has been proposed.[3] One problem, however, was the difficulty in specifying the amounts of the two geometrical isomers possible for ketimine **1**.



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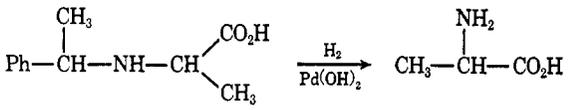
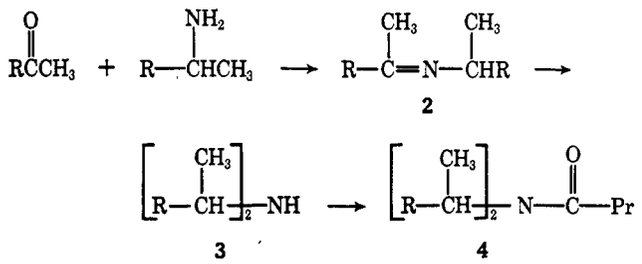


During the course of a synthesis of the amide **4**, we have observed a related case of asymmetric induction during the reduction of a ketimine with lithium aluminum hydride. In this case, the phenomenon was observed with optically inactive materials and the extent of the asymmetric induction was evident by glpc analysis of the two diastereoisomers present in the product. An explanation for the steric course of the reduction is presented which is based on the geometry of the ketimine **2**.



2

3 **4**

The ketimine **2**, resulting from condensation of 2-octanone and 2-aminooctane, was reduced with lithium aluminum hydride to give the amine **3** in 69% yield. When analyzed by glpc, the amine product showed two barely resolved peaks in a roughly 2:1 ratio on a 6 ft × $^1/_4$ in. Apiezon column. Acylation of the amine with butyryl chloride gave the amide **4**, which showed two peaks in a similar ratio. In the case of the amide, however, the two peaks were sufficiently well resolved to permit their separation by preparative glp, and in this way it was shown that the two peaks were due to diastereoisomers.

The two chiral centers in the amide **4** are probably closer to one another than are the chiral centers in the amine **3**. The greater interaction of symmetries in **4** presumably explains the ease of resolution of the diastereoisomers of **4** on a short-packed glpc column. The two isomers collected from preparative glpc were indistinguishable by ir, nmr, and tlc, while their mass spectra did show slight differences.

Before attempting to explain why the two diastereoisomers were produced in unequal amounts, it was first necessary to determine whether the major product from reduction of the ketimine **2** was the *meso* or the racemic form of the amine **3**. The racemic form should be resolvable on a glpc column containing an optically active liquid phase, and in fact Gil-Av[4] has reported the resolution of racemic amines as their trifluoroacetyl (TFA) derivatives on columns containing amino acid derivatives. Consequently, a 200 ft × 0.010 in. column was coated with the ureide of L-valine isopropyl ester. On this column, for example, the TFA derivative of 1-methylheptylamine gave two equal peaks due to the two enantiomers. However, all attempts to analyze the TFA derivative of bis(1-methylheptyl)amine (**2**) by this method were unsuccessful owing to excessive bleeding of the column above the recommended maximum temperature of 120°.

As an alternative method for distinguishing between the diastereoisomers, the amine **3** was acylated with an optically active acid chloride, N-trifluoroacetyl-L-prolyl chloride (TPC).[5] The product was analyzed on an 8 ft × $^1/_4$ in. column containing diethylene glycol succinate and showed three peaks. Two of these were equal in size and clearly resulted from the racemic diastereoisomer of the amine.

As further confirmation of the above peak assignment, the amine **3** was converted to its hydrochloride salt, which was recrystallized several times. When the amine was regenerated from the purified salt, the ratio of the two diastereoisomers was found to be significantly altered. The TPC derivative of this refined amine was analyzed as described above, and the size of the two equal peaks had changed relative to the third peak, confirming the earlier peak assignment.

Having thus distinguished between the two isomers, it was now evident that the racemate of **3** was the major product from reduction of the ketimine **2**, and in fact the racemate made up 62% of the isomeric mixture. Any explanation of this difference in the quantity of the diastereoisomers is complicated by the existence in the ketimine itself of two geometrical isomers, which is evident from its nmr spectrum. The olefinic methyl group of **2** appears as two distinct singlets at 8.30 and 8.16 ppm. The peak at 8.30 is much larger and is probably

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