in the usual manner. It was identified by melting point, mixture melting point, and infrared spectrum with XIIb, obtained by method A.

7-Chloro-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-Dioxide (XIb).—A solution of 21.3 g. (0.07 mole) of XIIb in 20 ml. of glacial acetic acid was hydrogenated at room temperature and atmospheric pressure in the presence of 1.8 g. of platinum oxide. After the absorption of 1.2 l. of hydrogen (21 hr.), the catalyst was removed by filtration, and the solution was evaporated to dryness under reduced pressure. The residue was dissolved in methylene chloride; the solution was washed with dilute alkali and concentrated to a volume of about 50 ml. The concentrate was passed over a column of 200 g. of Woelm aluminum (grade I), and the column was eluted with methylene chloride. The residue obtained from the first 250 ml. of eluate, after evaporation to dryness under reduced pressure, was treated with ether and yielded 7.9 g. (36%) of crystals. Recrystallization from ether gave XIb as colorless plates melting at 159–160.5°.

Anal. Calcd. for $C_{15}H_{14}ClNO_2S$: C, 58.53; H, 4.58. Found: C, 58.86; H, 4.56.

2,3-Dihydro-5-phenyl-1,4-benzothiazepine 1-Oxide (XVIIa).—To a stirred and cooled solution of 4.7 g. (0.02 mole) of Va in 100 ml. of methanol was added a solution of 4.2 g. (0.02 mole) of sodium periodate in 40 ml. of water. The mixture was stirred for 1 hr. at 30° and for 4 hr. at room temperature. The precipitated sodium iodate was removed by filtration, and the filtrate was concentrated to a small volume. The concentrate was extracted with methylene chloride; the organic layer was separated, dried, and evaporated to dryness under reduced pressure. The residue was treated with ether and yielded 3.5 g. (70%) of XVIIa, which, after recrystallization from ether, gave colorless prisms melting at 158–160°.

Anal. Calcd. for $C_{15}H_{13}NOS$: C, 70.56; H, 5.13. Found: C, 70.31; H, 5.00.

7-Chloro-2,3-dihydro-5-phenyl-1,4-benzothiazepine 1-Oxide (XVIIb). Hydrochloride.—Compound Vb (5.4 g., 0.02 mole) was dissolved in 200 ml. of methanol and oxidized with a solution of 4.5 g. (0.021 mole) of sodium periodate in 42 ml. of water by the procedure described for the synthesis of XVIIa. The reaction product was isolated as the hydrochloride (4.4 g., 67%). After recrystallization from methanol–ether, the hydrochloride of XVIIb was obtained as light yellow prisms melting at 206–207°.

Anal. Calcd. for $C_{15}H_{12}ClNOS \cdot HCl$: C, 55.52; H, 4.02. Found: C, 55.54; H, 4.34.

7-Chloro-2-(2-aminoethylsulfinyl)benzophenone Hydrochloride (XVIb).—A solution of 5.8 g. (0.02 mole) of XVIIb in 600 ml. of 3 *N* hydrochloric acid was heated on the steam bath for 4 hr., and the mixture was evaporated to dryness under reduced pressure. The residue, when treated with a mixture of ethanol and isopropyl alcohol, yielded 6.3 g. (92%) of crystals. After recrystallization from methanol–ether, XVIb was obtained as light yellow needles melting at 152–153°.

Anal. Calcd. for $C_{15}H_{14}ClNO_2S \cdot HCl$: C, 52.33; H, 4.39. Found: C, 52.32; H, 4.05.

2-Chloro-2,3-dihydro-5-phenyl-1,4-benzothiazepine (XVIIIa).—To a refluxing stirred solution of 4.7 g. (0.02 mole) of Va in 100 ml. of methylene chloride was added within 20 min. a solution of 1.6 ml. (0.021 mole) of sulfuryl chloride in 25 ml. of methylene chloride, and the mixture was refluxed for 1 hr. longer. The precipitated crystals were collected by filtration and dissolved in a mixture of methylene chloride and ice-cold dilute potassium hydroxide. The organic layer was separated, dried, and evaporated to dryness under reduced pressure, and the residue was treated with ether–petroleum ether to give 2.9 g. (54%) of crystals. After recrystallization from ether–petroleum ether, XVIIIa was obtained as colorless prisms melting at 93–94°.

Anal. Calcd. for $C_{15}H_{12}ClNS$: C, 65.80; H, 4.42. Found: C, 66.04; H, 4.40.

2,7-Dichloro-2,3-dihydro-5-phenyl-1,4-benzothiazepine (XVIIIb).—Compound XVIIb (18.5 g., 0.065 mole) was added in portions to 65 ml. of thionyl chloride. When the reaction had subsided, the solution was poured on ice, made alkaline with 50% potassium hydroxide, and extracted with methylene chloride. The organic layer was separated, dried, and evaporated to dryness under reduced pressure; the residue, on treatment with ether–petroleum ether, yielded 12 g. (60%) of crystals. After recrystallization from ether, XVIIIb was obtained as colorless prisms melting at 126–127°.

Anal. Calcd. for $C_{15}H_{11}Cl_2NS$: C, 58.45; H, 3.60. Found: C, 58.29; H, 3.32.

Acknowledgment.—We are indebted to Dr. V. Toome, Mr. S. Traiman, and Dr. F. Vane for the ultraviolet, infrared, and n.m.r. spectra and to Dr. Al Steyermark and his staff for the microanalyses.

Vilsmeier Formylation of 4-Dimethylaminostilbene

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Vilsmeier formylation of 4-dimethylaminostilbene using the complex prepared from phosphorus oxychloride and dimethylformamide gave 4-dimethylamino-α-phenylcinnamaldehyde (**2**) and 4-dimethylamino-3-formyl-α-phenylcinnamaldehyde (**3**). Formylation on the vinylene carbon atom, which results in the formation of **2** from 4-dimethylaminostilbene, also occurred with 4-dimethylamino-4′-nitrostilbene, giving rise to 4-dimethylamino-α-(4-nitrophenyl)cinnamaldehyde (**5**), but did not occur with 2,4-dimethoxystilbene. The latter gave the aromatic aldehyde 4,6-dimethoxy-3-stilbenecarboxaldehyde (**8**). The structure of the formylation products was established by chemical evidence, infrared, n.m.r. and mass spectrometry.

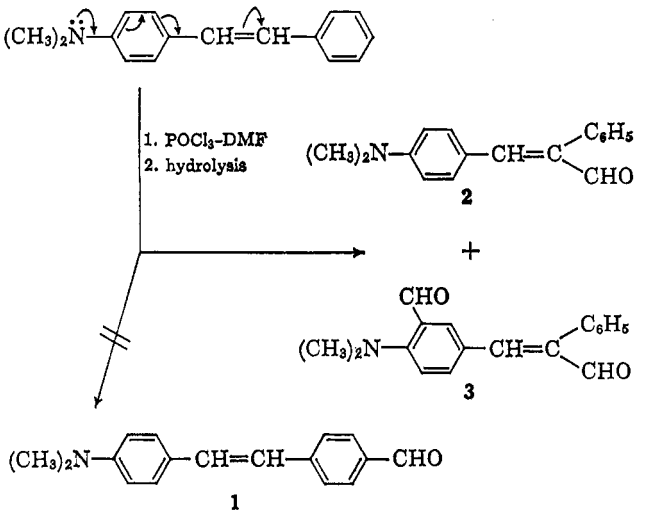
In connection with other work, it was desirable to develop a synthesis of the hitherto undescribed 4′-dimethylamino-4-stilbenecarboxaldehyde (**1**). The facile formylation of reactive aromatic and heterocyclic rings with the Vilsmeier complex[1] suggested the formylation of 4-dimethylaminostilbene as a possible synthetic route to **1**.

Results and Discussion

Formylation of 4-dimethylaminostilbene with the complex prepared from phosphorus oxychloride and dimethylformamide gave 4-dimethylamino-α-phenylcinnamaldehyde (**2**) and the diformyl derivative, 4-dimethylamino-3-formyl-α-phenylcinnamaldehyde (**3**). The use of 1 equiv. of complex led to the isolation of **2** in 33% yield; some dialdehyde **3** was formed and some starting material remained. The dialdehyde **3** was obtained in greatest yield (60%) by employing a large excess (4 equiv.) of complex and a long reaction time.

Structure **2**, 4-dimethylamino-α-phenylcinnamaldehyde, rather than **1** for the monoaldehyde, was suggested by examination of the infrared and n.m.r. spectra and was confirmed by chemical evidence. The infrared spectrum which failed to show the *trans* CH=CH

(1) For a recent review of the Vilsmeier reaction, see M.-R. DeMaheas, *Bull. soc. chim. France*, **112**, 1989 (1962).



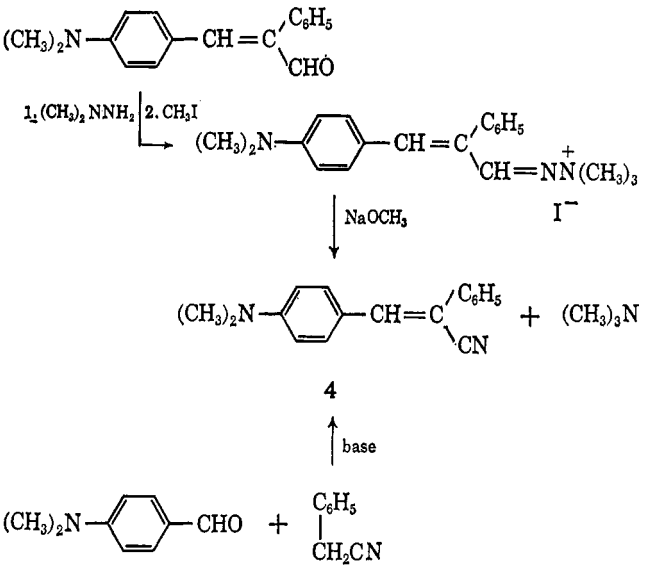
out-of-plane deformation band,[2] occurring at 965 cm.$^{-1}$ in 4-dimethylaminostilbene, and showing monosubstituted phenyl absorption, was incompatible with structure **1** and consistent with **2**.

The n.m.r. spectrum of the monoaldehyde established that the formyl group was not in the *ortho* position to the dimethylamino group. The spectrum showed a doublet, one-half of a typical A_2B_2 spectrum for a *p*-disubstituted benzene at δ = 6.55 and 6.40 p.p.m. for the aromatic hydrogens *ortho* to the dimethylamino group, and a singlet at 7.03 p.p.m. for the single olefinic hydrogen, the low field half of the A_2B_2 quartet falling into the region 7.15–7.50 p.p.m. with the remaining five aromatic hydrogens. The single aldehyde proton appears at δ = 9.64 p.p.m. and the dimethylamino hydrogens appear as a singlet at δ = 2.95 p.p.m. The ratio of the integrated area of the complex multiplet at 7.15–7.50 and the singlet at 7.03 p.p.m. to the one-half of the A_2B_2 at δ = 6.55 and 6.40 p.p.m. was 7.6:2, in good agreement with the required 8:2, demonstrating that the positions *ortho* to the dimethylamino group are substituted with hydrogen. Since the two olefinic hydrogens in the precursor, 4-dimethylaminostilbene, give rise to an AB quartet centered at 6.96 p.p.m. ($J \cong 9$ c.p.s., $\delta_{AB} \cong 0.1$ p.p.m.), the singlet at 7.03 p.p.m. in the monoaldehyde is evidence for the presence of the formyl group on the olefinic carbon atom.

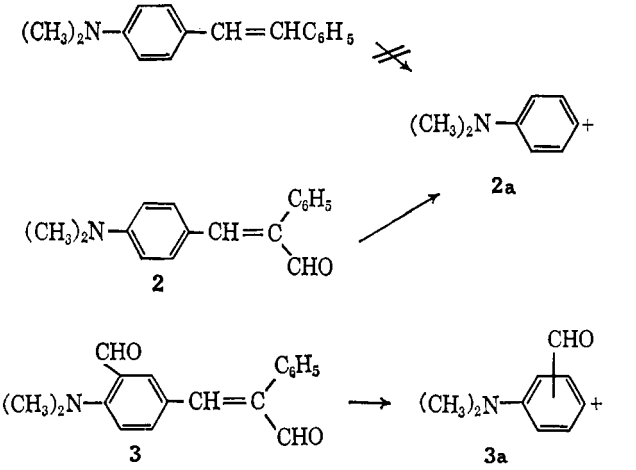
Structure **2** was confirmed by conversion to the corresponding nitrile **4** *via* the method of Smith and Walker,[3] indicated in the sequence shown. The nitrile obtained was found to be identical in all respects with 4-dimethylamino-α-phenylcinnamonitrile prepared by the base-catalyzed condensation of *p*-dimethylaminocinnamaldehyde with phenylacetonitrile, according to the method of Kauffmann.[4]

The structure of the dialdehyde **3** was established by elemental analysis, infrared, n.m.r., and mass spectrometry. The infrared spectrum showed carbonyl absorption at 1664 with a prominent shoulder at 1695 cm.$^{-1}$. The 1664-cm.$^{-1}$ absorption maximum of the dialdehyde agrees well with the absorption maximum of the monoaldehyde **2** at 1661 and the shoulder at 1695 cm.$^{-1}$ is in the proper range for an aromatic aldehyde.

(2) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1959, p. 45.
(3) R. F. Smith and L. E. Walker, *J. Org. Chem.*, **27**, 4372 (1962).
(4) H. Kauffmann, *Ber.*, **50**, 529 (1917).



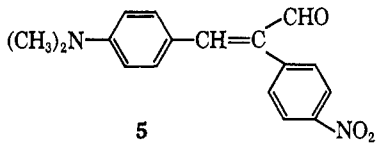
The second formyl group of the dialdehyde is assigned a position in the aromatic ring with the dimethylamino group, on the basis of the fragmentation pattern of the monoaldehyde and dialdehyde in the mass spectrometer. Whereas analysis of 4-dimethylaminostilbene in the mass spectrometer resulted in the detection of the molecular ion (M = 223), the monoaldehyde **2** gave the molecular ion (M = 251) and a major fragment with *m/e* 121; the dialdehyde (**3**) gave the molecular ion (M = 279) and a major fragment with *m/e* 149. Since the structure of **2** had already been established, the fragment having *m/e* 121 is unquestionably ion **2a**, and the fragment having *m/e* 149 resulting from the dialdehyde **3** undoubtedly has the structure **3a** because no fragments from possible isomers of **3**, in which the second aldehyde group is not in the dimethylamino ring, correspond to a mass of 149. Failure to detect ion **2a** from 4-dimethyl-



aminostilbene demonstrates that the observed fragmentation does not occur in the absence of a formyl group on the olefinic carbon atom, and the detection of fragment **3a** from the dialdehyde is evidence for the presence of the second formyl group in the dimethylamino ring. The n.m.r. spectrum of **3** showed a doublet at δ = 6.65 and 6.80 p.p.m. which is assigned as one-half of the AB portion of an ABX pattern for the 1,2,4-substituted benzene, the remaining aromatic signals from 7.05–7.70 p.p.m. obscuring the left half of the AB

pattern. The two aldehyde proton signals appear at δ = 9.73 and 9.88 p.p.m. and the dimethylamino protons appear as a singlet at 2.97 p.p.m. The ratio of the integrated area of the doublet to the aromatic signals at 7.05–7.70 p.p.m. is in agreement with the required 1:8, demonstrating that there is only one hydrogen atom *ortho* to the dimethylamino group. This is in complete agreement with the *ortho–para* directing influence of the dimethylamino group in electrophilic substitution.

Vinylene formylation was also observed for 4-dimethylamino-4′-nitrostilbene. The structure of the resulting aldehyde, 4-dimethylamino-α-(4-nitrophenyl)-cinnamaldehyde (**5**), was assigned on the basis of infrared and n.m.r. spectra. The infrared spectrum



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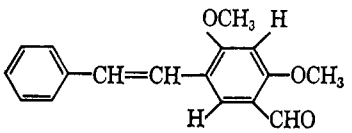

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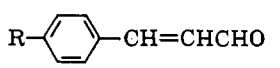
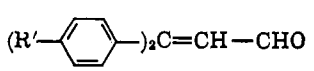
failed to show the *trans* CH=CH out-of-plane deformation band, occurring at 960–980 cm.$^{-1}$ in the stilbene precursor, and showed carbonyl absorption at 1670 cm.$^{-1}$. The n.m.r. spectrum shows two typical *p*-substituted phenyl A_2B_2 quartets: one is centered at δ = 6.85 p.p.m. (J = 9 c.p.s.) for the dimethylaminophenyl group; the other is centered at δ = 7.88 p.p.m. (J = 9 c.p.s.) for the *p*-nitrophenyl group. A singlet at δ = 7.42 p.p.m. superimposed on the high-field, "weak" member of the *p*-nitrophenyl quartet and of area equivalent to one hydrogen is assigned to the single olefinic hydrogen. The aldehyde proton appears at δ = 9.58 p.p.m. and the dimethylamino hydrogens appear at 3.07 ppm.

That formylation of 4-dimethylaminostilbenes gave the cinnamaldehyde derivatives rather than the aromatic stilbene–aldehydes is somewhat surprising and indicates that a relatively high electron density exists on the vinylene carbon atom owing to the strong mesomeric effect of the dimethylamino group. This mode of attack of the Vilsmeier reagent is reminiscent of the formylation of substituted and unsubstituted 1-aryl- and 1,1-diarylethylenes with this complex, to produce the corresponding substituted acroleins **6** and **7** as reported in the patent literature.[5]



6, R = H, OCH_3, $N(CH_3)_2$



7, R′ = H, Cl, OH, $N(CH_3)_2$

A number of electron-rich stilbenes were subjected to the Vilsmeier formylation reaction in the attempt to determine whether other electron-donating groups in the stilbene molecule would similarly direct attack of the reagent to the vinylene carbon atom. 4-Methyl-, 4-methoxy-, 4-hydroxy-, and 4,4′-dimethoxystilbenes were found to be insufficiently reactive to undergo Vilsmeier formylation and this behavior led to the recovery of starting material. In 2,4-dimethoxystilbene, the methoxyl groups occupy *ortho* and *para* positions in the same aromatic ring and thus serve to activate the same vinylene and aromatic carbon atoms. Formylation of 2,4-dimethoxystilbene did not occur on the vinylene carbon atom, but gave the aromatic aldehyde, 4,6-dimethoxy-3-stilbenecarboxaldehyde (**8**). This structure is supported by the infrared spectrum which shows *trans* CH=CH absorption at 966 and carbonyl absorption at 1680 cm.$^{-1}$. The n.m.r. spectrum unequivocally establishes the position of the aldehyde group. The two aromatic hydrogens in the substituted benzene ring appear as singlets at δ = 6.30 and 8.00 p.p.m. The large difference in chemical shifts is due to the different shielding provided by the adjacent groups. The methoxyl group appears as a singlet at δ = 3.78 p.p.m., the five remaining aromatic protons and two olefinic protons appear as a complex multiplet at δ = 7.05–7.60 p.p.m., and the aldehyde proton appears as a singlet at δ = 10.3 p.p.m. The absence of any coupling between the aromatic proton singlets at δ = 6.30 and 8.00 p.p.m. precludes assignment of any structure in which the hydrogens are *ortho* or *meta* to each other, and, hence, only structure **8** remains. The ratio of the integrated areas of the methoxyl singlet to the singlets at δ = 6.30 and 8.00 p.p.m. is 6:1:1.

Experimental

Melting points were taken in open capillaries and are corrected. Infrared spectra were obtained in potassium bromide with the Baird Model NK-1 recording spectrometer. Infrared absorption bands cited were of strong intensity unless otherwise indicated. N.m.r. spectra were obtained on a Varian A-60 spectrometer operating at 60 Mc. in deuteriochloroform solution, with tetramethylsilane as internal reference. Mass spectra were obtained on a 60° sector-type, single-focusing mass spectrometer equipped with an all-glass modification of the Caldecourt inlet,[6] heated to 235°.

Preparation of Substituted Stilbenes.—The stilbenes were prepared by the phosphonate condensation reaction,[7] a type of PO-activated olefination reaction originally reported by Horner and co-workers.[8] Either diethyl benzylphosphonate or diethyl *p*-nitrobenzylphosphonate was allowed to react with the appropriate aromatic aldehyde in dimethylformamide, with sodium methoxide as the base; yields were fair to good. Sodium methoxide was obtained from Fisher Scientific Co., diethyl *p*-nitrobenzylphosphonate and 2,4-dimethoxybenzaldehyde were obtained from the Aldrich Chemical Co., and diethyl benzylphosphonate and *p*-dimethylaminobenzaldehyde were Eastman grade.

4-Dimethylamino-α-phenylcinnamaldehyde (**2**).—4-Dimethylaminostilbene (22.3 g., 0.100 mole) suspended in 200 ml. of dimethylformamide was added, with stirring, to the complex prepared from phosphorus oxychloride (15.3 g., 0.100 mole) and 50 ml. of dimethylformamide. The temperature rose to 40° and a clear solution resulted. The reaction mixture was heated at 65° for 2–7 hr., allowed to stand overnight at room temperature, and finally decomposed by the cautious addition of 150 ml. of 10% sodium hydroxide solution and 150 ml. of water, with cooling. The solid was collected on a funnel, slurried with two 200-ml. portions of water, then 50 ml. of 50% aqueous methanol, filtered, and air dried to give 19.0 g. of yellow solid, m.p. 95–115°. Recrystallization from cyclohexane gave 8.2 g. (33%) of tiny yellow crystals of aldehyde, m.p. 131.5–134°. A second recrystallization from cyclohexane raised the melting point to 132.5–134.5°. Pertinent infrared bands were observed

(5) R. Wizinger, M. L. Coenen, and A. Bellefontaine, German Patent 865,440 (Feb. 2, 1953); *Chem. Abstr.*, **52**, 18322^h (1958).

(6) V. J. Caldecourt, *Anal. Chem.*, **27**, 1670 (1955).

(7) E. J. Seus and C. V. Wilson, *J. Org. Chem.*, **26**, 5243 (1961).

(8) L. Horner, H. Hoffmann, and H. G. Wippel, *Chem. Ber.*, **91**, 61 (1958).

at 1661, 820, and 710 cm.$^{-1}$, with no absorption in the 965–990-cm.$^{-1}$ region.

Anal. Calcd. for $C_{17}H_{17}NO$: C, 81.3; H, 6.8; N, 5.6. Found: C, 81.1; H, 7.2; N, 5.5.

The oxime was prepared in the conventional manner and had m.p. 186.5–188°.

Anal. Calcd. for $C_{17}H_{18}N_2O$: C, 76.7; H, 6.8; N, 10.5. Found: C, 77.1; H, 6.7; N, 10.7.

4-Dimethylamino-3-formyl-α-phenylcinnamaldehyde (3).—4-Dimethylaminostilbene (22.3 g., 0.100 mole) was added, with stirring, to the complex prepared from phosphorus oxychloride (61.2 g., 0.400 mole) and 200 ml. of dimethylformamide. A dark, clear solution resulted. The reaction mixture was heated at 70° for 16 hr., then decomposed by the cautious addition of 600 ml. of 10% sodium hydroxide solution. The solid was collected on a funnel, slurried with 200 ml. of water, and air dried to give 16.8 g. (60%) of yellow product, m.p. 103.5–105.5°. Recrystallization from methanol–water gave 12.2 g. of yellow crystals of dialdehyde, m.p. 106.5–108.5°. A second recrystallization from methanol–water raised the melting point to 108–109.5°. Pertinent infrared bands were observed at 1664 (shoulder at 1695), 820 (m), 810 (m), 715, and 700 cm.$^{-1}$ (m). There was no absorption in the region 965–990 cm.$^{-1}$ but there was a medium-weak band at 960 resulting from 1,2,4 aromatic substitution.[9]

Anal. Calcd. for $C_{18}H_{17}NO_2$: C, 77.4; H, 6.1; N, 5.0. Found: C, 77.2; H, 6.0; N, 5.1.

The dioxime was prepared in the conventional manner and had m.p. 191–193°.

Anal. Calcd. for $C_{18}H_{19}N_3O_2$: C, 69.9; H, 6.15; N, 13.6. Found: C, 69.8; H, 5.8; N, 13.5.

Proof of Structure of 4-Dimethylamino-α-phenylcinnamaldehyde (2).—4-Dimethylamino-α-phenylcinnamaldehyde (1) was converted to 4-dimethylamino-α-phenylcinnamonitrile (4) following the procedure of Smith and Walker.[3] The 4-dimethylamino-α-phenylcinnamonitrile consisted of yellow plates having a melting point of 134.5–135.5°. The infrared spectrum of this material and that of the same compound prepared according to Kauffmann[4] by the condensation of phenylacetonitrile with *p*-dimethylaminobenzaldehyde were superimposable. The mixture melting point of the two samples was not depressed on admixture.

4-Dimethylamino-α-(4-nitrophenyl)cinnamaldehyde (5).—4-Dimethylamino-4′-nitrostilbene (5.0 g., 18.7 mmoles) was formylated by essentially the same procedure used to prepare **2**, but with 2 equiv. of the complex prepared from phosphorus oxychloride and dimethylformamide and heating the reaction mixture at 70° for 4.5 hr. Decomposition of the reaction mixture, followed by recrystallization of the crude product from methanol, gave 1.4 g. (25%) of tiny, brick red needles having a melting point of 148–152°. A second recrystallization from methanol raised the melting point to 155–156.5°. Pertinent infrared bands were observed at 1670, 825, and 720 cm.$^{-1}$. There was no absorption in the region 965–990 cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{16}N_2O_3$: C, 68.9; H, 5.4; N, 9.45. Found: C, 68.7; H, 5.4; N, 9.3.

4,6-Dimethoxy-3-stilbenecarboxaldehyde (8).—2,4-Dimethoxystilbene (12.0 g., 50.0 mmoles) was formylated by essentially the same procedure used to prepare **2**, but with 2 equiv. of the complex prepared from phosphorus oxychloride and dimethylformamide and heating the reaction mixture at 70° for 17.5 hr. Decomposition of the reaction mixture, followed by recrystallization of the crude product from methanol, gave 5.2 g. (39%) of tiny yellow prisms, m.p. 122–124.5°. Recrystallization from ethanol gave tiny, pale yellow needles, having m.p. 123–125°. Pertinent infrared bands were observed at 1680, 966 (m), 815, 755, and 695 cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.1; H, 6.0. Found: C, 76.2; H, 6.0.

Acknowledgment.—The author wishes to express his gratitude to Dr. T. H. Regan and Mr. D. P. Maier, of the Analytical Chemistry Department, for the n.m.r. and mass spectral work.

(9) See ref. 2, p. 82.

Solvent Significance in the Mechanism of Direct Acylation. Reactions in Cyclic Ethers[1]

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Received January 23, 1965

The mechanism of direct acylation in anhydrous *p*-dioxane was studied, using L-leucine and dichloroacetyl chloride as the model system, and comparisons are drawn with earlier work in ethyl acetate. Because of its influence on kinetic interpretation, the solubility of L-leucine was investigated in several solvents. The effects of a number of parameters on either the reaction rate or the solubility of the amino acid in the organic solvent were determined. The kinetic data for the reaction in *p*-dioxane fit the same differential equation developed earlier for the ethyl acetate system, which accords with the apparent over-all similarity of the reaction in the two different solvent types. However, the specific reaction intermediates that can be reasonably suggested for both systems are at considerable variance with each other. Several amino acids not previously acylated by this procedure were converted to products and the number of solvents allowing this over-all reaction type has been increased.

In the initial investigation of the mechanism of direct acylation[3] the kinetics in dry ethyl acetate for the reaction between L-leucine and dichloroacetyl chloride were shown to fit closely to a differential equation which was developed from theoretical considerations. Because of its pertinence to the kinetic study, the solubility of L-leucine in the solvent under various conditions was investigated and the reaction was observed to proceed in other ester acetates. This initial study permitted the suggestion of a proposed reaction intermediate, which is essentially an anhydride type formed between the original acyl chloride and the enol form of the acetate ester. The present work was undertaken to investigate other potential solvents, to compare such reactions with the acetate (ethyl) system and to explore further aspects of the mechanism and nature of this heterogeneous reaction in which the rate of dissolution of the suspended, crystalline reactant (the amino acid or related compound) is rate controlling. *p*-Dioxane was one of the several "new" solvents found

(1) Presented in part before the Division of Biological Chemistry at the 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept. 1964.

(2) Excerpted from the thesis submitted by D. E. H. in partial fulfillment of the requirements for the degree of Master of Science.

(3) (a) E. Ronwin and C. B. Warren, *J. Org. Chem.*, **29**, 2276 (1964). (b) In the derivation of this equation, the surface area, S, appears in the intercept because the generally accepted equilibrium situation between a solid dissolving in a liquid and the reverse crystallization process is given by (using the symbols applicable to this case) $k_4S = k_5[L_s]S$ and *not* by $k_4S = k_5[L_s]$. See G. H. Nancollas and N. Purdie, *Quart. Rev.* (London), **18**, No. 1, 13 (1964).