mainder of the product. Crystallization from ethanol–ether gave **19** (4.0 g, 76%): mp 195° dec; ν_{CO} 1750, 1640 cm^{-1}; nmr peaks (DMSO-d_6) at δ 12.3 (s, 1 H), 9.5 (d, 2 H), 8.6 (d, 2 H), 7.9–7.0 (m, 4 H), 6.0 (s, 1 H), 4.31 (q, 2 H), 3.4 (s, 2 H), and 1.32 (t, 3 H).

Anal. Calcd for $C_{18}H_{17}BrN_2O_3$: C, 55.52; H, 4.37; N, 7.19. Found: C, 55.68; H, 4.31; N, 7.10.

***N*-Carbethoxymethyl-4-(1-methylindol-2-ylcarbonyl)pyridinium Bromide** (**20**).—A solution of **9** (2.4 g, 0.010 mmol) in anhydrous tetrahydrofuran (50 ml) was treated with 10 ml of ethyl bromoacetate with stirring. The solution was refluxed for 2 hr, cooled, and diluted with ether. The orange precipitate was recrystallized several times from ethanol–ether giving **20** (3.6 g, 89%): mp 166.5–167.5° dec; ν_{CO} 1750, 1640 cm^{-1}; nmr peaks (DMSO-d_6) at δ 9.48 (d, 2 H), 8.6 (d, 2 H), 7.0–7.9 (m, 5 H), 6.0 (s, 2 H), 4.0–4.5 (overlapping q and s, 5 H), 1.30 (t, 3 H).

Anal. Calcd for $C_{19}H_{19}BrN_2O_3$: C, 56.58; H, 4.71; N, 6.95. Found: C, 56.33; H, 4.77; N, 6.92.

Mass Spectral Data.—The principal ions in the mass spectra of compounds **2c**, **2d**, **2g**, **2i**, **9**, **10**, **11**, **12**, **13**, and **17** have been submitted in tabular form as supplementary data in the microfilm edition of this jouranl.[27]

Registry No.—**1a**, 33037-72-8; **1b**, 33037-73-9; **1e**, 33037-74-0; **1f**, 33037-75-1; **1h**, 33037-76-2; **2b**, 948-65-2; **2e**, 18132-19-9; **2d**, 33037-79-5; **2f**, 24512-42-3; **2g**, 33037-81-9; **3**, 33037-82-0; **4**, 33037-83-1; **5**, 33037-84-2; **6**, 33037-85-3; **7**, 33037-86-4; **8**, 33037-87-5; **9**, 25387-27-3; **10**, 33037-89-7; **11**, 33080-10-3; **12**, 33037-90-0; **13**, 33037-91-1; **14**, 33037-92-2; **15**, 33037-93-3; **17**, 33037-94-4; **18**, 33037-95-5; **19**, 33037-96-6; **20**, 33037-97-7.

[27] Mass spectral data will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to author, title of article, volume, and page number. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

Isocarbostyrils from Monomeric and Dimeric β-Styryl Isocyanates[1,2]

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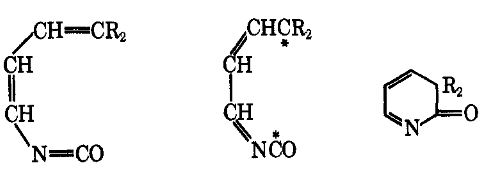
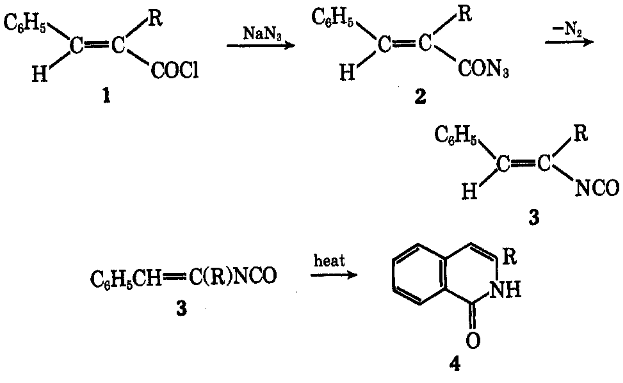
In an inert solvent at 250°, *trans*-β-styryl isocyanate (**3a**) and its β-methyl (**3b**) and β-phenyl (**3c**) derivatives were efficiently isomerized into the corresponding isocarbostyril **4a**, **4b**, and **4c**. In the presence of iodine the reaction proceeded conveniently at the reduced temperature of 140°. Two dimers of β-styryl isocyanate were obtained; one was converted into **4a** on heating in refluxing pyridine.

A formal, but unestablished, interconversion by valence isomerization may be recognized for an *s-cis*-isocyanatobutadiene-1,3 and a 2-oxo-2,3-dihydropyridine. Should ring closure proceed instead from either a zwitterionic or diradical structure, then the geometrical restriction on the isocyanate disappears. Styryl isocyanates were selected for investigation since ring closure from closely related systems was known[3] and they are more readily available than structurally simpler isocyanatodienes.



* = ± or ·

By the thermal Curtius reaction each *trans*-cinnamoyl azide (**2**), obtained by treating *trans*-cinnamoyl chloride (**1**) with sodium azide, gave the corresponding *trans*-β-styryl isocyanate (**3**) in overall yield ranging from moderate to good. The azide could, however, be converted into the isocarbostyril without isolation of **3**.



a, R = H; **b**, R = CH_3; **c**, R = C_6H_5

Each isocyanate was efficiently isomerized in mineral oil or diphenyl ether at 250°. The isomerization **3a** → **4a** in the presence of iodine occurred in dichlorobenzene at 180° or in *m*-xylene at 140°, but there was no reaction in carbon tetrachloride at 77° and *trans*-isocyanate was quantitatively recovered.[4] Reaction progress in *o*-dichlorobenzene was monitored not only by disappearance of ir absorption at 2260 cm^{-1} (NCO), but also by development, followed by disappearance, of ir absorption (*o*-dichlorobenzene solution) at 1740 cm^{-1} and by development of permanent bands at 1665 and 1650 cm^{-1}. This indicated that the forma-

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[1] Financial assistance was received from NASA Grant No. NGR-012-114.

[2] G. J. Mikol and J. H. Boyer, Abstracts, 160th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1970, ORGN 51.

[3] The present investigations were completed when F. Eloy and A. Deryckere [*J. Heterocycl. Chem.*, 1191 (1970); *Chim. Ther.*, 48 (1971)] reported the preparation pf pyridine, isoquinoline, and other heterocyclic derivatives by the thermal cyclization of vinyl isocyanates substituted in the β position by a vinyl radical. H. M. Blatter and H. Lukaszewski [*Tetrahedron Lett.*, 855 (1964)] report a similar thermal cyclization for $C_6H_5N{=}C(C_6H_5)NCS$ and discuss similar cyclizations for $C_6H_5N{=}C(C_6H_5)NCO$ and for $C_6H_5C(C_6H_5){=}C(C_6H_5)CH{=}C{=}O$.

[4] L. Crombie, *Quart. Rev., Chem. Soc.*, **6**, 101 (1952), reviews methods for geometrical isomerization.

TABLE I

PREPARATION AND PROPERTIES OF AZIDES 2 AND ISOCYANATES 3

$C_6H_5CH{=}C(X)Z$

		2, Z = CON_3[a]				3, Z = NCO[b]			
Form, X	1, Z = COCl, Mp, °C	Mp, °C	Yield, %	Nmr, δ	Ir, cm^{-1}	Bp, °C (mm)	Yield, %	Nmr, δ	Ir, cm^{-1}
a, H	33.5–34.5[c]	84–86[d]	72	7.68[e] 6.46[e]	2143[f]	44–45[g] (0.10)	81	6.58[h] 6.31[h]	2260[i]
b, CH_3	49–50[j]	k		7.61[l] 2.05[m]	2140[f]	57–59[n] (0.17)	78	6.20[o] 2.05[p]	2255[i]
c, C_6H_5	Oil[q]	70–72[r]	49	7.90[s]	2150[f]	t	37[u]	6.50[s]	2250[i]

[a] Each azide was prepared from the corresponding acyl chloride, assumed to be trans, and sodium azide according to a general procedure described by P. A. S. Smith, in "Organic Reactions," Vol. III, R. Adams, Ed., Wiley, New York, N. Y., 1946, p 373, but with acetonitrile as solvent. [b] Each isocyanate was prepared by heating the corresponding acyl azide in refluxing benzene according to a general procedure described by M. O. Forster, *J. Chem. Soc.*, 433 (1909), with the added precaution of purging with nitrogen before and during pyrolysis. [c] As obtained from Distillation Products, Rochester, N. Y. [d] L. W. Jones and J. P. Mason, *J. Amer. Chem. Soc.*, **49**, 2528 (1927), reported mp 86°. [e] Trans vinyl protons with J_{ab} = 16 Hz. [f] Azido group. [g] M. O. Forster (ref *b*) reported bp 107° (12 mm). [h] Trans vinyl protons with J_{ab} = 15 Hz. [i] Isocyanate group. [j] J. A. Moore, *J. Org. Chem.*, **20**, 1607 (1955), reported mp 49–50°. In the present work the preparation followed a general procedure reported by H. E. Zimmerman, L. Singer, and B .S. Thyagarajan, *J. Amer. Chem. Soc.*, **81**, 108 (1959). [k] The preparation was carried out below 10°. A quantitative yield of impure product which solidified at 0° and melted with decomposition at room temperature could not be purified for analysis. On a silica gel column there was appreciable decomposition, but about 50% of the azide was eluted with hexane–benzene (4:1). [l] Vinyl proton quartet, J_{ac} = 1.5 Hz. [m] Methyl protons as a doublet, J_{ac} = 1.5 Hz. [n] Mp 27–28°. *Anal.* Calcd for $C_{10}H_9NO$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.36; H, 5.82; N, 8.76. [o] Vinyl proton quartet, J_{ac} = 1.2 Hz. [p] Methyl protons as a doublet, J_{ac} = 1.2 Hz. [q] R. Riemschneider and H. Kampfer, *Monatsh. Chem.*, **90**, 518 (1959), reported mp 47–48°. The preparation here followed a general procedure (see ref *j*). [r] The preparation was carried out below 10°. The product was obtained initially as an oil which solidified on cooling. Apparently heat of crystallization was sufficient to cause nitrogen evolution. It melted with decomposition. It was not purified for analysis. Trituration with hexane removed isocyanate and other impurities. [s] Vinyl proton singlet. [t] The isocyanate undergoes ring closure on heating. [u] Eluted with benzene–hexane (3:2) from a silica gel column containing crude product.

tion of **4a** might be proceeding from either an isocyanate monomer **3a** or one of its dimers **5a**.

A solid dimer **5a**, mp 167–168°, ir 1725 and 1650 cm^{-1} (chloroform solution), was isolated from a reaction carried out in a mixture of *m*-xylene and carbon tetrachloride (15:1) containing a trace of iodine. Absence of absorption near 2260 cm^{-1} (NCO) required the dimerization to consume isocyanato groups. It was converted into **4a** by heating in diphenyl ether or in pyridine. Refluxing **3a** in a mixture of benzene and pyridine did not convert the isocyanate to **4a**; another dimer **5a′**, mp 229–230°, was the only product isolated.

Whether or not the separate conversions of an isocyanate and its dimer into an isocarbostyril are unrelated or proceed from a common intermediate has not been determined. In either event the ring closure required for isocarbostyril formation could be available either from a zwitterionic or diradical intermediate or from a cis olefin by valence isomerization. The present data tends to disallow a concerted valence isomerization, since cyclization is subject to catalysis.

Experimental Section

Instrumental data were obtained from a Beckman IR-10 and/or a Perkin-Elmer Model 521 infrared spectrometer, a Varian A-60A nmr spectrometer, and a Perkin-Elmer Model 270 mass spectrometer except where noted. Melting points were determined with a Thomas-Hoover capillary apparatus. Both melting points and boiling points are uncorrected. Elemental analyses were obtained from Microtech Laboratories, Skokie, Ill. The preparation of styryl isocyanates is described in Table I.

Thermal Reactions of β-Styryl Isocyanates 3.—A solution of 725 mg (5 mmol) of *trans*-β-styryl isocyanate (**3a**) in 4 ml of mineral oil (Fisher Scientific Company No. 13639) was heated at 240–250° for 4 hr. Isocarbostyril (**4a**) was isolated by precipitation on cooling and by dilution with hexane. The solid product, 688 mg, 95%, after trituration with hexane, recrystallized from ethanol as tan needles, mp 205–207°, ir ($CHCl_3$) 3440 (NH), 1660 (C=O), and 1640 cm^{-1} (C=C). A mixture melting point with an authentic sample showed no depression and the ir spectrum was superimposable on the spectrum obtained from authentic material. Isocarbostyril (**4a**) was obtained in 70% yield from a similar treatment of **3a** in refluxing diphenyl ether, bp 250°, for 2.5 hr.

In a similar way in mineral oil at 240–250°, 3-methylisocarbostyril (**4b**), 80% yield, mp 208–210°, ir ($CHCl_3$) 3420 (NH),1660 (C=O), and 1650–1670 cm^{-1} (C=C), was obtained from *trans*-β-(β-methyl)styryl isocyanate (**3b**), and 3-phenylisocarbostyril (**4c**), 75% yield, mp 197–198°, ir ($CHCl_3$) 3420 (NH), 1660 (C=O), and 1645 cm^{-1} (C=C), was obtained from *trans*-β-(β-phenyl)styryl isocyanate (**3c**), prepared *in situ* by heating α-phenylcinnamoyl azide (**2c**) in mineral oil at 80°.

β-Styryl isocyanate (**3a**) was prepared *in situ* by heating cinnamoyl azide (**2a**), 1.2 g (6.94 mmol) in refluxing carbon tetrachloride for 4 hr (or until ir monitoring showed disappearance of absorption for the azido group). Continued heating for 24 hr at the reflux temperature after adding a few flakes of iodine produced no change in the trans isocyanate. After replacing the solvent with *m*-xylene to which a flake of iodine was added, heating at the reflux temperature, 139°, for 166 hr brought about slow development of an absorption peak at 1740 cm^{-1} (C=O). Removal of solvent left a solid residue from which a small amount of colorless needles, mp 167–168° after recrystallization from acetonitrile, was obtained: ir ($CHCl_3$) 3300–2800, 1725 (C=O), 1650, 1640, 1628 (C=C), and 1410 cm^{-1}; nmr ($CDCl_3$) δ 6.0–7.0 (C_6H_5), 5.77 and 7.30 (doublets, J_{ab} = 8 Hz), and 5.52 and 6.78 (doublets, J_{ab} = 15 Hz). It appears to be a dimer (**5a**) of β-styryl isocyanate. *Anal.* Calcd for $(C_9H_7NO)_2$: C, 74.46; H, 4.86; N, 9.64; mol wt, 290.4. Found: C, 74.51; H, 4.91; N, 9.47; mol wt (osmometric), 262.

A similar treatment of *trans*-β-styryl isocyanate (**3a**) in refluxing *o*-dichlorobenzene, bp 179°, to which a flake of iodine was added brought about disappearance of absorption at 2260 cm^{-1} while a new carbonyl band initially developed at 1740 cm^{-1} (solvent was *o*-dichlorobenzene), but after 4 hr began to disappear as a band at 1665 cm^{-1} developed. Isocarbostyril (**4a**), mp 204–207°, was isolated in 90% yield. The solid dimer **5a**, mp 167–168°, ir 1725 cm^{-1} ($CHCl_3$), was also transformed into isocarbostyril in 34% yield on heating in refluxing diphenyl ether for 15 min, the time required for disappearance of the 1725-cm^{-1} absorption band and development of absorption at 1660 cm^{-1}.

A different dimer (**5a′**) of β-styryl isocyanate was obtained. After generating the isocyanate *in situ* by heating 2.4 g (13.9 mmol) of cinnamoyl azide in 25 ml of refluxing benzene for 4 hr, 0.7 ml of pyridine was added and the solution was heated at reflux for 190 hr. On standing at room temperature for 7 days a granular solid, 0.62 g, 38.7%, separated. Recrystallization from a mixture of ethyl acetate and acetonitrile gave colorless needles: mp 229–230°; ir ($CHCl_3$) 3030, 1705 (C=O), 1430 and 960 cm^{-1}; nmr (CH_3COCH_3) δ 7.2–7.8. *Anal.* Calcd for $(C_9H_7NO)_2$: C, 74.46; H, 4.86; mol wt, 290.4. Found: C, 74.25; H, 4.91; mol wt, 325 (osmometric).

In contrast the dimer **5a**, mp 167–168°, on heating in pyridine for 1 hr was transformed into isocarbostyril; its ir (pyridine) absorption was identical with a spectrum for authentic material in pyridine.

Registry No.—**2a**, 33066-17-0; **2b**, 33066-18-1; **2c**, 32528-95-3; **3a**, 33066-20-5; **3b**, 33066-21-6; **3c**, 33066-22-7; **4a**, 491-30-5; **4b**, 7114-80-9; **4c**, 7115-13-1; **5a**, 33041-36-0.

The Reaction of Acyl Cyanides with Grignard Reagents

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The reaction of benzoyl cyanide (**1**) with Grignard reagents occurs *via* addition to the carbonyl group to give the corresponding phenyl ketones **2** in good yield. Acetyl cyanide (**3**), however, reacts with aliphatic Grignard reagents predominantly by reduction of the carbonyl group and subsequent acylation by **3** to give cyano ester **5**. Carbonyl cyanide (**6**) is attacked by isopropylmagnesium bromide at carbonyl to give isobutyryl cyanide, which is further reduced and acylated to give isobutyraldehyde cyanohydrin and its isobutyl ester. Finally, **6** reacts with phenylmagnesium bromide by attack at both the carbonyl and cyano groups to give benzil, benzophenone, and minor amounts of benzonitrile and benzoyl cyanide. These variations in reaction selectivity are discussed in light of the mechanisms postulated, and INDO calculations of electron density and infrared stretching frequencies are brought to bear on the reactivity of these compounds.

Part A

The reaction of Grignard reagents with carboxylic acid derivatives has been extensively investigated;[2] one apparent exception to this is the acyl cyanide derivative. Some time ago we began an investigation of acyl cyanide and carbonyl cyanide reactions with Grignard reagents in order to answer the following questions. (1) Would these compounds react as "deactivated" acid chlorides; *i.e.*, would the cyano group act exclusively as a carbonyl activating group, or would it compete with the organometallic reagent? (2) Would the intermediate cyanohydrin magnesium salt (I or IV in eq 1 or 2) have sufficient stability to block further addition to the carbonyl group, thus permitting the synthesis of ketones, or would it compete with the carbonyl group in reaction with the organometallic reagent? (3) Could sequential addition to carbonyl cyanide be controlled to permit synthesis of unsymmetrical ketones?[3] The answers to these questions constitute the subject of this two-part paper.

We began by investigating the reactions of benzoyl cyanide (**1**) and acetyl cyanide (**3**) to determine the selectivity of carbonyl addition. Reaction of **1** with a variety of Grignard reagents proceeded as expected; the corresponding phenyl ketones **2a–c** were obtained in 65–84% yield when **1** was treated with 1 equiv of the organomagnesium compound in ether at −40°. Gas chromatographic analyses of the crude products showed <5% of the tertiary alcohol and no trace of product derived from addition to the cyano group of **1**. Similarly, reaction of **3** with phenylmagnesium bromide at −70° resulted in a 70% yield of **2a**. When **3** was allowed to react with isopropyl-, *n*-amyl-, or cyclohexylmagnesium bromide, however, a new product **5** was isolated in 58–77% yield in addition to minor amounts of the expected ketone. The structure of **5** was confirmed by nmr and by synthesis of an authentic sample; its mode of formation is postulated in eq 1 ($R = R' = CH_3$). It is apparent that, in the case of **3**, reduction of the carbonyl group *via* hydride transfer predominates over addition. There was no evidence of addition or reduction at the cyano group of **3**.

Reaction of carbonyl cyanide **6** with Grignard reagents also occurred by distinct pathways depending on the nature of the organomagnesium reagent. It should of course be noted that products resulting from reduction of **6** would be sufficiently volatile to escape detection under the reaction conditions. When **6** was treated with 1 equiv of isopropylmagnesium bromide in ether at −70°, **7** and **8** were isolated in 51 and 21% yield, respectively. The initial step in both cases involves addition at carbonyl and subsequent elimination of cyanide to give isobutyryl cyanide II as an intermediate. Reduction of II as in the case of **3** followed by trapping of the cyanohydrin magnesium salt I by **6** or II leads to the cyanohydrin esters (for R′ = CN, eq 2, the cyanoformate hydrolyses in water to give the cyanohydrin **7**).

When **6** was treated with phenylmagnesium bromide in ether at −70°, however, four identifiable products were obtained as a result of addition at *both* the carbonyl and cyano groups: benzil (**9**), 49%; benzophenone (**10**), 19%; benzonitrile (**11**), 8%; and benzoyl cyanide (**12**), 5%. The formation of these products is postulated in eq 2; addition to the cyano group predominates over addition to carbonyl in **6** by 2.4 to 1. We have postulated the formation of **11** as occurring *via* intermediate III rather than IVa on the basis of the fact that IVb rapidly eliminates cyanide to give II (and ultimately **7** and **8**) under the reaction conditions. Thus, IVa would be expected to collapse to **12** before addition of a second phenyl group could occur. When phenyllithium was used as the organometallic reagent, **11** was the only detectable product,

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[1] (a) Alfred P. Sloan Foundation Fellow; (b) taken in part from the Ph.D. thesis of S. R. L., University of Minnesota, 1971.

[2] M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Non-Metallic Substances," Prentice-Hall, New York, N. Y., 1954, pp 709–724.

[3] During the course of this work an excellent general method for unsymmetrical ketone synthesis was reported; for a review see D. Seebach, *Synthesis*, **1**, 17 (1969).