Chemistry of Heterocyclic Compounds. 22. Condensation Reactions of 2-Substituted Pyridines[1a,b]

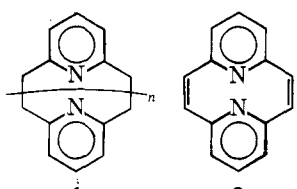
George R. Newkome* and J. Michael Robinson[1c]

Department of Chemistry, Louisiana State University, Baton Rouge, Louisiana 70803

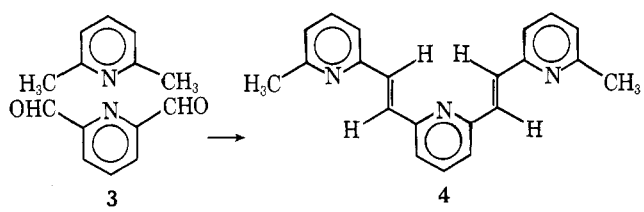
Received January 20, 1976

Condensation reactions of 2-substituted pyridines were investigated as model systems which would afford insight into possible synthetic routes to the 2,6-pyridino macrocyclic series 1 and 2. While phenylacetic acid and deoxybenzoin (15) reacted with benzaldehyde (8) under Perkin and Knoevenagel conditions, respectively, to form predominantly the *E* olefin (with the desired cis-phenyl rings), ethyl 2-pyridylacetate (7) and α-(2-pyridyl)acetophenone (17) reacted with 2-pyridinecarboxaldehyde (10) to afford almost exclusively the *Z* isomer (with trans-pyridyl rings). A mechanism explaining the predominance of the undesired *Z* isomer in these heterocyclic systems is proposed.

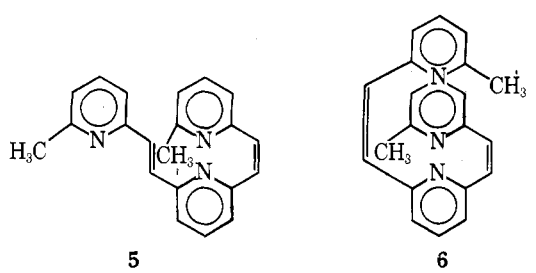
As part of a continuing study of open- and closed-chain polypyridines, one of our initial goals was the construction of [2,2. . .]pyridinophanes (1 and 2). At the onset of this work,



1 2



3 4



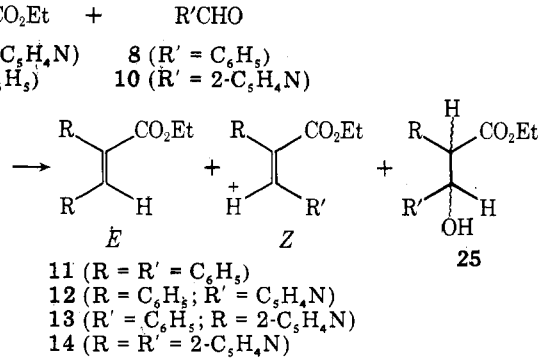
5 6

several members of 1 had been prepared albeit in low yields by means of a Wurtz coupling reaction under high dilution.[2] During the course of this investigation, Boekelheide and Lawson[3] reported the successful synthesis of 2 (n = 1) through a novel double ring contraction of a disulfide macrocycle. Earlier an unsuccessful attempt[2b] to prepare 2 (n = 1) by condensation of 2,6-dimethylpyridine with 2,6-pyridinedicarboxaldehyde (3) in the presence of acetic anhydride was reported; however, the open-chain trans,trans diene 4 was isolated and later confirmed to possess two trans linkages.[4] Under diverse conditions, condensations of simple 2-methylpyridines with aromatic aldehydes have been reported[5] to afford predominantly the corresponding trans olefins. Conversely, the well-known Perkin[6] and Knoevenagel[7] condensations of arylacetic acids and α-arylacetophenones, respectively, with substituted benzaldehydes have been shown to give α,β-unsaturated carbonyl compounds with the cis-phenyl orientations in excellent yields. Thus, we herein report our preliminary data on the condensation of simple heterocyclic esters and ketones with various aldehydes in order to ascertain the applicability of these condensation reactions to the construction of pyridinophanes.

Results and Discussion

Condensations of 2-methylpyridines with 2-pyridinecarboxaldehydes have afforded stilbazoles (2-styrylpyridines) which generally possess the *E* configuration. In light of our synthetic goals, we desired procedures which will permit construction of this linkage with the *Z* configuration (cis orientation of the heterocyclic rings); therefore, the utilization of either the Perkin condensation or the Knoevenagel reaction might afford a procedure to the disubstituted acrylates and 1-phenyl-2-propenones, which possess a predominance of the desired cis hetero-ring orientation.

Substituted Acrylates. Bragg and Wibberley[9] reported the condensation of ethyl 2-pyridylacetate (7) with benzal-



RCH_2CO_2Et + $R'CHO$

7 (R = 2-C_5H_4N) 8 (R′ = C_6H_5)
9 (R = C_6H_5) 10 (R′ = 2-C_5H_4N)

E *Z* 25

11 (R = R′ = C_6H_5)
12 (R = C_6H_5; R′ = C_5H_4N)
13 (R′ = C_6H_5; R = 2-C_5H_4N)
14 (R = R′ = 2-C_5H_4N)

dehyde using a catalytic amount of piperidine and isolation (46%) of cinnamate 13 containing the desired *E* orientation (cis rings) about the double bond. Those authors unfortunately subjected the reaction mixture to rigorous distillation conditions, then reported the isolation of a single picrate derivative in an unspecified yield and no confirmatory spectral data. Repetition of their original procedure, as best possible, was carried out until the purification stage; in order to prevent thermal degradation, a combination of both thin and thick layer chromatography was used to isolate the products. Although two products, *E*- and *Z*-12, were isolated in 20 and 10%, respectively, the major component (43%) was the unreacted ester 7. NMR analysis of the initial reaction mixture substantiated this product distribution (see Table III) and supported the slight predominance of the *E* isomer, thus partially confirming the previous results.[8]

Similarly, ethyl 2-pyridylacetate was condensed with the more reactive 2-pyridinecarboxaldehyde (10) in the presence of piperidine to afford (~70%) 14 in less than half of the time required for the reaction with benzaldehyde. However, in this case the *Z* isomer was isolated in a 2:1 predominance over the corresponding *E* isomer. Small amounts (2%) of the intermediate alcohols 25 as well as starting ester (7) were also recovered. Reaction of 7 and 10 under standard Perkin condi-

Table I. Selected Spectral and Physical Data for the Substituted Ethyl Acrylates[a]

Registry no.	Compd	Mp or bp, °C (mm)	Ir, cm^{-1} [b] >C=O	Ir, cm^{-1} [b] >C=C<	Uv, nm ($\epsilon \times 10^3$)[c]		NMR, δ, ppm[d] >=<H	NMR, δ, ppm[d] $-OCH_2-$	NMR, δ, ppm[d] $-CH_3$
7042-31-1	*E*-11	30–31[e]	1710	1625	219 (16.4)	284 (14.8)	7.79	4.15	1.14
59169-48-1	*E*-12	195–203 (4)	1713	1644	250 (10.1)	292 (11.7)	7.93	4.26	1.24
24832-45-9	*E*-13	179–186 (2.5)[f]	1712	1630		281 (15.8)	7.93	4.28	1.26
59169-51-6	*E*-14	145–150 (3.5)	1714	1591	257 (10.9)	291 (11.3)	7.97	4.27	1.26
2048-32-0	*Z*-11	135–140 (0.1)[g]	1723	1604	222 (14.3)	287 (20.8)	6.99	4.24	1.14
59169-49-2	*Z*-12	69.5–71.5	1722[h]	1620	223 (10.9)	304 (16.7)	6.91	4.41	1.29
59169-50-5	*Z*-13	150–160 (0.15)	1723	1586	220 (11.6)	299 (18.5)	7.67	4.33	1.18
59169-52-7	*Z*-14	77.5–79	1723[h]	1587	263 (12.4)	311 (23.6)	7.67	4.46	1.35

[a] Satisfactory analytical data (±0.4% for C, H, and N) were obtained for all new compounds in this table. [b] Thin films, except where noted. [c] Methanol solvent. [d] Deuteriochloroform solvent, ca. 10% w/v. [e] Lit.[13] mp 31–32 °C. [f] Lit.[9] bp 160–161 °C (1 mm). [g] Lit.[13] bp 130 °C (0.01 mm). [h] Chloroform solvent.

Table II. Selected Spectral and Physical Data for the Substituted Benzoylethylenes[a]

Registry no.	Compd	Mp, °C	Ir, cm^{-1} [b] >C=O	Ir, cm^{-1} [b] C–O	Uv, nm ($\epsilon \times 10^3$)[c]	
7474-65-9	*E*-19	100.5–101.5[d]	1645	1250	255 (16.5)	295 (14.4)
59169-53-8	*E*-20					
34236-72-1	*E*-21	155–157[e]	1668[f]		257 (16.3)[g]	318 (16.4)[g]
59169-55-0	*E*-22	86.5–88.5	1644	1265	268 (13.5)	297 (15.9)
59169-57-2	*E*-23	185.5–186.5[h]	1645	1265	266 (18.2)	289 (18.2)
59169-59-4	*E*-24	Oil	1659	1259	259 (14.2)	293 (12.2)
7512-67-6	*Z*-19	86–87.5[i]	1659	1225	254 (23.5)	282 (21.1)
59169-54-9	*Z*-20	157.5–158.5	1670	1232	256 (21.9)	303 (18.9)
3423-64-1	*Z*-21	168–168.5[j]	1672[f]		251 (21.6)[g]	328 (20.4)[g]
59169-56-1	*Z*-22	115–116	1682	1240	258 (21.5)	297 (21.5)
59169-58-3	*Z*-23	135–136[k]	1689	1225	251 (22.4)	327 (22.4)
59169-60-7	*Z*-24	154–155.5	1687	1243	254 (21.7)	310 (21.2)

[a] Satisfactory analytical data (±0.4% for C, H, N) were obtained for all new compounds in this table. [b] Nujol mulls. [c] Methanol solvent. [d] Lit.[20] mp 99–101 °C. [e] Lit.[20] mp 155–157 °C. [f] In carbon tetrachloride.[20] [g] In ethanol (95%).[20] [h] Lit.[7a] mp 188–189.5 °C. [i] Lit.[20] mp 85–87 °C. [j] Lit.[20] mp 167–168 °C. [k] Lit.[7a] mp 135–136 °C.

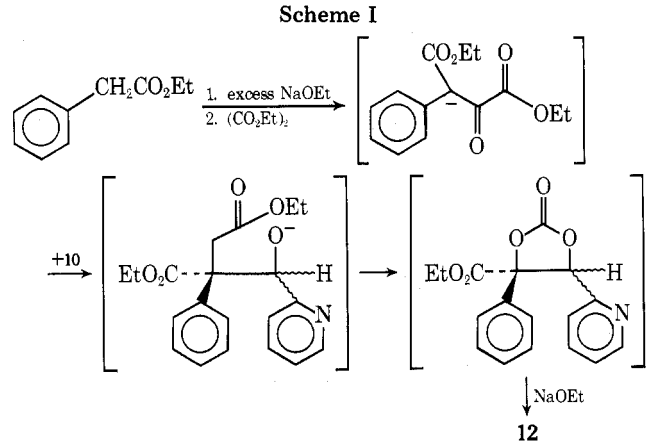
tions, i.e., triethylamine and acetic anhydride at room temperature, gave a similar 2:1 ratio of *Z* to *E* isomer distribution along with the acetate of **25**. This latter product resulted from use of the mild reaction conditions. In all of the reactions in which acetic anhydride was used, 3-substituted propenoic acids were detected but not isolated. In the absence of acetic anhydride, triethylamine in absolute ethanol affected the condensation of **7** and **10** resulting in an increased predominance (3:1) of the *Z* isomer. The intermediary alcohol **25** was also detected but not isolated. The NMR analysis as well as actual product isolation (Table III) showed a similar *Z* to *E* product distribution (ca. 2–3 to 1), thus indicating no distinct advantage to any of these procedures.

Numerous attempts to condense ethyl phenylacetate (**9**) with **10** under varied reaction conditions failed. Others have reported similar results.[9] In order to complete this series as well as by-pass the low acidity of the α proton of **9**, acrylates *E*- and *Z*-**12** were synthesized by a procedure described by Shahak[10] (Scheme I). Although both isomers of **12** were isolated in low yield, the *E* isomer was isolated in predominance. This product distribution probably results from steric approach control of the intermediate carbanion on **10**; the intermediates were not isolated.

For comparative purposes, the α-phenylcinnamates **11** were prepared by various literature procedures.[11–14] Selected physical and spectral data for **11–14** are given in Table I.

Disubstituted Benzoylethylenes. Deoxybenzoin (**15**), α-(4-nitrophenyl)acetophenone (**16**), and α-(2-pyridyl)acetophenone (**17**) were each condensed with either **8** or **10**; the

Scheme I



12

physical and spectral data for the resultant products are listed in Table II. In general, these α-substituted acetophenones were reacted with a slight excess of the appropriate aldehyde in the presence of a catalytic amount of piperidine. Benzene was used as solvent, rather than ethanol, which permitted the azeotropic removal of water. The product distribution for the various reactions is summarized in Table III.

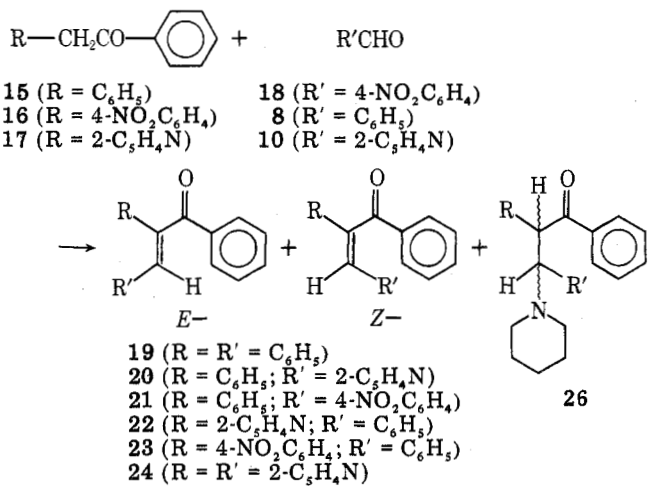
When benzaldehyde is used, these condensation reactions proceed smoothly with a catalytic amount of piperidine; however, with 2-pyridinecarboxaldehyde, an equivalent amount of piperidine was necessary to realize the theoretical amount of water and to ensure completion of the reaction. In these cases, the piperidine underwent a Michael addition with

Table III. Summary of Product Distribution

Reaction prepn of	Method	Yield, % Isolated E-	Isolated Z-	Isolated Other components	Estimates from NMR data E-	Estimates from NMR data Z-	Estimates from NMR data Other components
11[a]		60	11		78	22	
12	A, B			**9** (>95)			
	D	16	9	**9** (>70)	*b*	*b*	*b*
13	A	20	10	**7** (43)	30	12	**7** (~50)
14	A	20	45	**7** (13), **25** (2)	24	50	**7** (16), **25** (4)
	B		46		23	50	**7** (<10), **25** acetate (18)
	C		49		~17	60	**7** (10), **25** (18)
19	E	74	26				
20	E	0	67	**26** (27)	<5	~70	**26** (~30)
	F	0		**27a** (71), **27b** (15)			
22	E	0	74	**26** (traces)	<5	>90	**26** (traces)
23	E[c]	25	62		29	70	
	E[d]	9	64	**15** (5)	13	69	**15** (6)
24	E	0	30	**26** (15)	<5	~50	**26** (~20)[e]

[a] Values cited were derived from condensation of the corresponding acid. [b] Not available. [c] With crude benzaldehyde, traces of benzoic acid. [d] With freshly distilled benzaldehyde. [e] Other components were detected but not characterized.

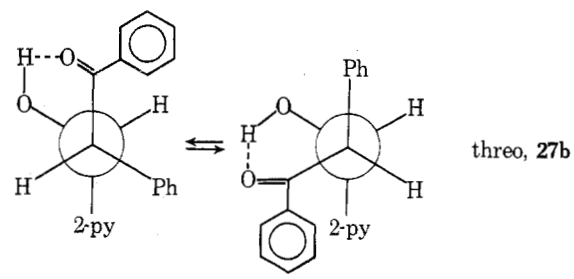
the condensation product; therefore, the adduct had to be refluxed with dilute mineral acid to effect elimination of piperidine and generate the desired olefin. For example, when deoxybenzoin (**15**) and **10** were condensed in the presence of

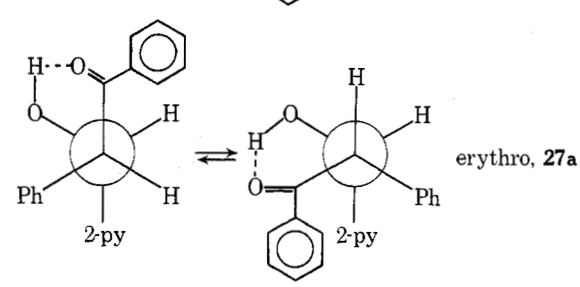


an equivalent amount of piperidine, the piperidine adduct **26** was isolated in 27% yield. This compound apparently decomposes to the *Z* isomer on extended heating, since *Z*-**20** was isolated in 67% yield by refluxing the reaction mixture. Adduct **26** smoothly underwent β-elimination of piperidine in refluxing 5% hydrochloric acid to generate exclusively (91%) *Z*-**20**.

In order to assign the structure to this initial piperidine adduct **26**, a sample was partially isomerized (26%) at elevated temperatures. The erythro and threo isomers of **26** were separated. Since the vicinal methine coupling constant in the NMR spectrum of the initial adduct is 11.5 Hz compared with 10.5 Hz for the thermally derived isomer the structures were at best tentatively assigned to the threo and erythro isomers, respectively.

To circumvent this addition product, **15** and **10** were condensed in the presence of a tertiary or highly hindered secondary amine catalysis. The intermediate alcohols **27a** and **27b** were isolated in 72 and 15% yield, respectively. The NMR spectrum of the major alcohol showed a methine coupling constant of 5 Hz, while for the minor isomer the coupling constant was 7.5 Hz. This methine–hydrogen coupling can be





rationalized using the Newman projections of the most stable conformations of **27a** and **27b**, noting the repulsion of the largest groups as well as hydrogen bonding. With the aid of these drawings, the isomer with the larger coupling constant would be the threo isomer. Thus, the major alcohol (**27a**) isolated in this condensation reaction has the smaller coupling constant and is probably the erythro isomer. Indeed, the erythro isomer was expected to predominate.[7b,15] Further substantiation of the structural assignment is available by comparison to similar systems.[16] Also, **27a** was heated to 150 °C for several hours and upon cooling **27b** was isolated as the major thermodynamic product.

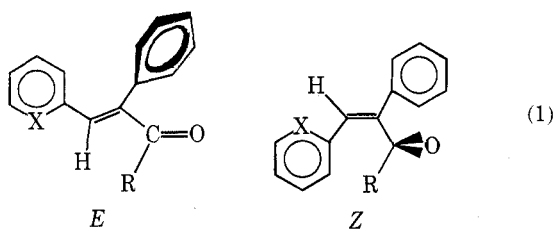
Photochemical Isomerization. The *E* isomers in Table II were prepared in more suitable quantities by mild photoisomerization of the readily available corresponding *Z* isomer. A 0.01 M benzene solution of the respective *Z* isomer under an argon atmosphere in Pyrex was allowed to stand in sunlight for approximately 6 h.[7a] In this way, *E*-**22** and *E*-**24** were prepared and isolated in 30% yield. The photolysis mixture containing *E*- and *Z*-**20** could not be separated. From preliminary experiments, it was found that more dilute solutions irradiated for longer periods of time resulted in increased photoisomerization. For example, *E*-**13** was obtained from the corresponding *Z* ester in 88% yield by photolysis of a 0.001 M

solution for 72 h. Alternate procedures for photoisomerization of substituted (*Z*)-2-stilbazoles are well documented.[5e,17]

The olefinic lability of the *E* isomers which possess a β-2-pyridyl group is supported by the fact that neither **20** or **24** could be isolated in the pure form. Nucleophilic attack at the β position (Michael addition) is an extremely facile process. Such reactions have been previously reported during attempted isolation of 3- and/or 4-(2′-pyridyl)cyclopentadienones[18] and 2-aryl-3-(2′-pyridyl)acrylonitriles.[19] During attempted molecular distillation, *E*-**24** underwent a thermal decomposition; however, spectral data were obtained on a freshly chromatographed sample.

Isomeric Relationships of the Acrylates and Disubstituted Benzoylethylenes. Structural assignments of the α,β-unsaturated esters and ketones in Tables I and II, respectively, were based on NMR, ir, and uv spectral data as well as by comparison of the spectral data of several well-known analogues, e.g., **21** and **23.** Although each spectral method might enable distinction between the *E* and *Z* isomers, these tabular combinations provide unequivocal structural assignments. Black and Lutz[7a] have discussed the reactivity and uv spectral data for the related α-phenylchalcones; further confirmation of their assignments was provided by ir and uv data.[20] Likewise, the configuration of the acid precursors to **11** was well established.[12]

The carbonyl absorption for the nonconjugated *Z* esters and ketones generally appeared at a higher frequency than that of the corresponding *E* isomer, approximately 10 and 25–40 cm^{-1}, respectively. The C–O stretching frequency of the *E* ketones and the carbon–carbon double bond stretching frequency both absorb at a higher frequency owing to increased conjugation expected in the *E* isomer.



(1)

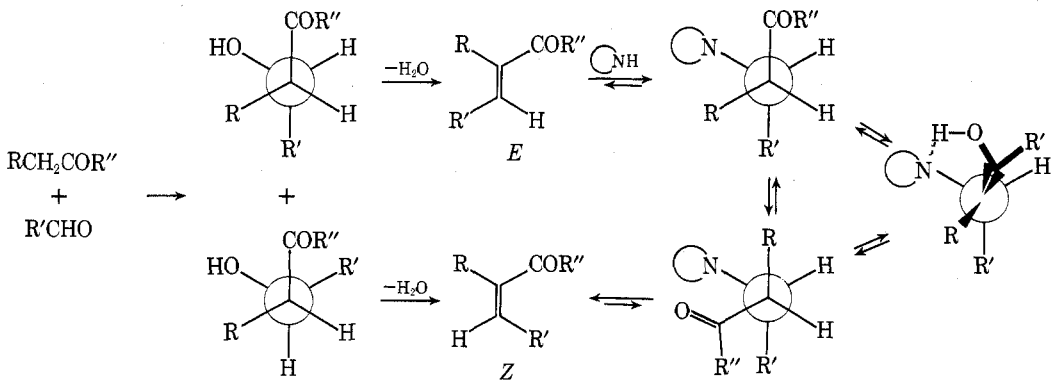
X = N or CH
R = Ph or OEt

With the exception of **13,** the uv data in Tables I and II exhibited a higher λ_{max} for each *Z* isomer as well as a larger molar extinction coefficient. This general effect was more pronounced at the longer wavelength absorption band. The exception of **13** is attributed to the difficulty in isolation and purifying the samples; this spectral method is less useful in these heterocyclic systems owing to the sensitivity to trace impurities.[22]

The NMR spectrum of the α,β-unsaturated ketones exhibited only a broad aromatic region in which the vinylic hydrogen resonance was superimposed and indistinguishable. Isomeric differentiation was possible for the esters (see Table I). Although the methyl group of the ester exhibited no difference in chemical shifts which could be related to olefinic stereochemistry, the methylene function exhibited an isomeric distinction in $CDCl_3$ solvent.[21] Since the *Z* isomer carbonyl group is less effectively conjugated (eq 1), the methylene resonance was shifted downfield by 5–18 Hz compared to the *E* isomer. The vinylic proton resonance can be easily characterized as a sharp spike. The cis relationship between the carbonyl group and vinylic proton in the *E* isomer resulted in the appearance of a more deshielded vinylic resonance (δ 7.0–7.7). The vinylic hydrogens of *Z*-**13** and *Z*-**14,** which have the 2-pyridyl group cis to the vinylic proton, were also more deshielded (ca. 0.7 ppm) than the corresponding *Z*-**11** and *Z*-**12,** which possess a cis phenyl–vinylic hydrogen relationship. The pyridine nitrogen lone pair has been shown to effect this magnitude of deshielding within a range of 0.5–0.7 ppm.[24]

Conclusions

Table III shows both the percentages of actual products and NMR spectral percentages of the initial reaction mixture. Although acrylates **12** and **13** give a slight preference for the desired *E* isomer, the 1:2 (*E* to *Z*) distribution shown for **14** indicates that the increased electron withdrawal of the 2-pyridyl moiety causes an isomerization in the later stages of the reaction via either (1) abstraction–equilibration of the α proton of an intermediate, or (2) Michael addition, followed by isomerization, and elimination. A better insight into the mechanistic course can be shown for the benzoylethylenes. The alcohol intermediate **27** (**a** and/or **b**) loses water with "stereoelectronic overlap" control[6a] to initially generate the *E* isomer. Since the *E* olefin is effectively conjugated through the coplanar carbonyl, verified by the spectral data, a facile Michael addition at the β carbon of the α,β-unsaturated carbonyl system occurs.[7a] Furthermore, piperidine undergoes such addition to the *E* isomer,[18,19] whereas no addition products are derived from the *Z* isomer. A similar facile nucleophilic 1,4 addition ($NaBH_4$) has been recently reported[23] for methyl (*E*)-α-(*p*-nitrophenyl)cinnamate (reaction time 10 min), whereas the *Z* isomer required about 8 h for complete reduction. Subsequently, the piperidine adduct can undergo equilibration to the more stable isomer, followed by β-elimination resulting in formation of the *Z* isomer. Thus, Michael addition and subsequent elimination equilibrates the *E* and *Z* isomer. However, if such an equilibrium exists under these conditions, it is dramatically shifted toward the *Z* isomer in **20, 22,** and **24,** and to a lesser extent with the 2-pyridyl acrylates. Since the *Z* olefin resembles a trans stilbene, nucleophilic addition would be greatly diminished. Indeed, both *E*- and *Z*-**19** can be equilibrated with a 10 molar excess of piperidine at 80 °C for 24 h to afford the same 72:28 ratio of *Z*- to *E*-**19;** a ratio which is closely aligned to ours.



Thus, in both the Perkin and Knoevenagel reactions in which products possess a 2-pyridyl moiety, an increased *Z* to *E* ratio is experienced over the corresponding model compounds.

We are currently attempting multiple-sequential condensation reactions of 2,6-pyridinedicarboxylates and 2,6-pyridinedicarboxaldehydes in order to gain access to systems **1** and **2**.

Experimental Section

Melting points were measured in capillary tubes with a Thomas-Hoover Unimelt and are reported uncorrected. NMR (60 MHz) spectra were measured in deuteriochloroform solvent and recorded on either a Varian Associates A-60A or a Perkin-Elmer R12-B spectrometer. All chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane (~1%) as the internal standard. Ir spectra were recorded on either a Perkin-Elmer 137 or a Perkin-Elmer 621 grating spectrophotometer. Uv spectra were determined in absolute methanol on a Cary 14 recording spectrophotometer; absorbance values were reported in wavelength (nm) followed by molar extinction coefficient (ϵ). Elemental analyses were performed by either Mr. R. Seab in these laboratories or by Galbraith Laboratories, Inc., Knoxville, Tenn.

Preparative thick layer chromatography (THLC) utilized Brinkmann PF-254+366 silica gel of 2-mm thickness. Reported frontal retention (R_f) values were obtained from thin layer chromatography utilizing Brinkmann HF-254+366 silica gel of 0.25-mm thickness; the solvent system for both thin and thick layer methods was identical. Dry column chromatography used nylon tubing and Waters Associates dry column grade silica gel, activity III. All solvents and reagents were dried and either distilled or recrystallized by standard procedures.

Substituted Ethyl Acrylates. Selected spectral data for these acrylates are compiled in Table I.

Ethyl (*Z*)- and (*E*)-2,3-Di(2′-pyridyl)acrylates (14). Method A. Piperidine–Ethanol. A mixture of ethyl 2-pyridylacetate[25] (2.66 g, 16.1 mmol), 2-pyridinecarboxaldehyde (1.72 g, 16.1 mmol), and piperidine (1 ml) in 25 ml of absolute ethanol was refluxed for 12 h. The solvent and excess volatile reagents were removed in vacuo affording an oil, which was dissolved in ether–petroleum ether (bp 30–60 °C), decolorized, and allowed to crystallize, giving 980 mg (25%) of *Z*-**14**, mp 77.5–79 °C.

Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.50; H, 5.30; N, 10.95.

The mother liquor (3 g) was chromatographed on a column of silica gel with cyclohexane–ethyl acetate (3:1) and using gradient elution to pure ethyl acetate. Combined fractions afforded an additional 820 mg of *Z*-**14**, 350 mg of ethyl 2-pyridylacetate, 800 mg (20%) of *E*-**14** [bp 145–150 °C (3.5 mm)], and 86 mg (2%) of the intermediary alcohols.

Anal. Calcd for $C_{15}H_{14}N_2O_2$ (*E*-**14**): C, 70.85; H, 5.55. Found: C, 70.73; H, 5.60.

Method B. Acetic Anhydride–Triethylamine. A solution of ethyl 2-pyridylacetate (3.31 g, 20 mmol), 2-pyridinecarboxaldehyde (2.15 g, 20 mmol), triethylamine (25 ml), and acetic anhydride (25 ml) was stirred at 25 °C under nitrogen for 15 h. The mixture was poured into ice water, basified with solid sodium carbonate, and extracted with ether. The ether layer was dried over anhydrous sodium sulfate and concentrated. NMR analysis of the residue indicated <23% of *E*-**14**, 50% of *Z*-**14**, and traces of acetylated intermediary compounds (ca. 18%). The residue was dissolved in dichloromethane, conveniently decolorized through a small silica gel column, and recrystallized from cold ether–petroleum ether to give 2.32 g (46%) of *Z*-**14**, mp 77–78 °C.

Method C. Triethylamine–Ethanol. An ethanol solution of ethyl 2-pyridylacetate (3.31 g, 20 mmol), 2-pyridinecarboxaldehyde (2.14 g, 20 mmol), and triethylamine (20 ml) was refluxed under nitrogen for 16 h. The solvents and volatile reactants were removed in vacuo and NMR analysis of the residue indicated 18% of alcoholic intermediates, 17% of *E*-**14**, 60% of *Z*-**14**, and ~10% starting ester. Recrystallization of the decolorized residue gave 2.5 g (50%) of *Z*-**14**, mp 77.5–79 °C.

Ethyl (*Z*)- and (*E*)-2-(2′-pyridyl)cinnamate (13) were prepared from ethyl 2-pyridylacetate (505 mg, 3.06 mmol) and redistilled benzaldehyde (358 mg, 3.38 mmol) via method A. After removal of the solvents and excess volatile reagents, the residue was chromatographed (THLC) with cyclohexane–ethyl acetate (2:1), affording *Z*-**13** [78 mg, 10%; bp 150–160 °C (0.15 mm); R_f 0.63; methiodide mp 223–225 °C (dec), lit.[8] mp 227–228 °C (dec)], *E*-**13** [(154 mg, 20%; bp 179–186 °C (2.5 mm), lit.[8] bp 160–161 °C (1 mm)], unreacted starting ester (216 mg; 43%; R_f 0.41), and several trace unidentified compounds.

Ethyl (*Z*)- and (*E*)-2-Phenyl-3-(2′-pyridyl)acrylate (12). Method A. Piperidine–Ethanol. A mixture of ethyl phenylacetate (3.0 g, 20 mmol), 2-pyridinecarboxaldehyde (2.1 g, 20 mmol), and piperidine (1 ml) in 25 ml of absolute ethanol was refluxed for 12 h. After standard workup procedures, the unreacted starting materials were recovered (>95%).

Method B. Acetic Anhydride–Triethylamine. The above procedure was followed except for the substitution of acetic anhydride (15 ml) and triethylamine (15 ml) for the base and solvent. After standard workup the starting ester and aldehyde were recovered (>95%).

Method D.[10] A mixture of ethyl phenylacetate (1.64 g, 10 mmol), diethyl oxalate (1.46 g, 10 mmol), and sodium hydride (270 mg, 11.2 mmol) in 50 ml of di(*n*-butyl) ether was warmed at 65–70 °C for 1 h. The ethanol was removed in vacuo; then after cooling to less than 50 °C, 2-pyridinecarboxaldehyde (1.09 g, 10 mmol) was added and the mixture was refluxed under nitrogen for 1 h. The reaction mixture was cooled, poured into ice water, extracted with chloroform, washed successively with a 10% sodium carbonate solution, water, and saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated. The residue was chromatographed (THLC) with cyclohexane–ethyl acetate (2:1) affording *Z*-**12** (145 mg; 9%; mp 69.5–71.5 °C; R_f 0.60), *E*-**12** [253 mg; 16%; bp 195–203 °C (4 mm); R_f 0.54], unreacted ethyl phenylacetate (70%), and several minor unidentified compounds.

Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found (*Z* isomer): C, 75.76; H, 5.82; N, 5.71. Found (*E* isomer): C, 75.68; H, 5.82; N, 5.46.

(*Z*)- and (*E*)-2-phenylcinnamic acids were prepared by standard Perkin procedures[11] from phenylacetic acid and benzaldehyde. The utilization of Fieser's method[12] for isomer separation afforded pure *Z* acid (11%; mp 138–139 °C, lit.[12] 138–139 °C) and *E* acid (59.5%; mp 172–173 °C, lit.[12] mp 174 °C).

Ethyl (*E*)-2-Phenylcinnamate. The *E* acid was esterified using standard acid-catalyzed conditions and workup. The residual oil was recrystallized from diethyl ether–hexane (1:1) affording pure *E*-**11**, mp 30–31 °C (lit.[13] mp 31–32 °C).

Ethyl (*Z*)-2-Phenylcinnamate. Prolonged esterification for the preparation of *Z*-**11** from the acid was obviated by an adaptation of Mills' procedure.[14] A mixture of (*Z*)-2-phenylcinnamic acid (1.26 g, 5.63 mmol), ethyl iodide (870 mg, 5.60 mmol), and triethylamine (550 mg, 5.45 mmol) was refluxed under nitrogen for 7 h. After cooling, the mixture was extracted with anhydrous ether and concentrated. The residue was suspended in ethyl acetate, filtered through activated alumina, and concentrated to give 853 mg (62%) of pure *Z*-**11**, bp 135–140 °C (0.1 mm) [lit.[13] bp 130 °C (0.01 mm)].

Substituted 1,2-Diarylbenzoylethenes. Selected spectral and melting point data for these benzoylethenes are compiled in Table II.

Deoxybenzoin was prepared by the method of Kohler and Nygaard:[26] mp 54.5–55.5 °C (lit.[26] mp 55 °C); NMR δ 4.23 (s, $COCH_2$, 2 H), 7.1–7.6 (m, ArH, 10 H); ir (Nujol) 1675 cm^{-1} (C=O).

2-(4′-Nitrophenyl)acetophenone was prepared by an established procedure:[27] mp 142–143.5 °C (lit.[27] mp 144 °C); NMR δ 6.40 (s, $COCH_2$, 2 H), 7.2–7.75 (m, ArH, 5 H), 7.9–8.35 (m, *o*-BzH and 3′,5′-ArH, 4 H); ir (Nujol) 1689 (C=O), 1225 and 1208 cm^{-1} (C–O).

α-(2-Pyridyl)acetophenone was prepared (69%) by an established procedure,[28] bp 149–155 °C (2 mm), mp 54–56 °C (cyclohexane) (lit.[28] mp 52.5–54 °C).

General Condensation for 1,2-Diaryl Benzoylethylenes. Method E. Piperidine–Benzene. A mixture of 2-arylacetophenone (25 mmol), arylaldehyde (29 mmol), and piperidine (0.1 ml) in 25 ml of dry benzene was refluxed under nitrogen. After 5–14 h, the theoretical amount of water had been collected utilizing a Dean-Stark separator. Solvent and excess volatile reagents were removed in vacuo. The residue was decolorized and recrystallized usually from ethanol–ether. The mother liquors were concentrated and chromatographed (THLC). Yields were essentially quantitative.

Condensation of Deoxybenzoin with 2-Pyridinecarboxaldehyde. Method E. Piperidine Catalyst. Materials were condensed by the above general procedure and after refluxing for 19 h, the NMR spectrum of the reaction mixture indicated 20% completion. Addition of 1 ml of piperidine followed by another 2 h of reflux gave an additional amount of water. Finally, addition of a slight molar excess of piperidine gave rise to the theoretical amount of water after 6 h. The solvent and excess volatile reagents were removed in vacuo and the residue was recrystallized from ether–ethanol affording 2.38 g (27%)

of 1-phenyl-2-*N*-piperidino-2-(2′-pyridyl)benzoylethane (**26**): mp 167.5–169 °C; NMR δ 0.85–1.70 (m, 3,4,5-pip-**H**, 6 H), 1.95–2.95 (m, 2,6-pip-**H**, 4 H), 4.72 (d, pyr-C**H**–, J = 11.5 Hz, 1 H), 5.84 (d, PhC**H**–, J = 11.5 Hz, 1 H), 6.80–7.65 (m, Ar**H**, 11 H), 8.00–8.25 (m, *o*-Bz**H**, 2 H), 8.47–8.65 (m, 6-pyr-H, 1 H); ir (Nujol) 1673 (C=O), 1592, 1219, 763, and 699 cm^{-1}.

Anal. Calcd for $C_{25}H_{26}N_2O$: C, 81.04; H, 7.08; N, 7.56. Found: C, 80.64; H, 6.97; N, 7.47.

The mother liquor was concentrated affording 4.79 g (67%) of *Z*-**20**: NMR δ 6.77–7.68 (ArH and vinyl H, m, 12 H), 7.83–8.10 (*o*-BzH, m, 2 H), 8.13–8.32 (6-pyr-H, m, 1 H). Other spectral data are listed in Table II.

Anal. Calcd for $C_{20}H_{15}NO$: C, 84.18; H, 5.30; N, 4.91. Found: C, 84.13; H, 5.18; N, 4.89.

The piperidine adduct (1.11 g, 30 mmol) in 30 ml of 5% hydrochloric acid was refluxed overnight, poured into ice water, basified with a 10% sodium carbonate solution, extracted with chloroform, and dried with anhydrous magnesium sulfate. Concentration afforded a residue which was recrystallized from 95% ethanol providing 780 mg (91%) of pure *Z*-**20**.

All new 1,2-diarylbenzoylethenes listed in Table II were prepared via method E. NMR spectral data and pertinent microanalyses for these new compounds follow: *E*-**19** [NMR δ 7.05–7.57 (m, ArH and vinyl H, 14 H), 7.83–8.08 (m, *o*-BzH, 2 H)]; *Z*-**22** [NMR δ 6.95–7.75 (m, ArH, 11 H), 7.85–8.15 (m, *o*-BzH, 2 H), 7.92 (s, vinyl H, 1 H), 8.50–8.68 (m, 6-pyr-H, 1 H)]; *Z*-**24** [NMR δ 6.82–7.78 (m, ArH, 9 H), 7.85–8.35 (m, *o*-BzH, 2 H), 7.92 (s, vinyl H, 1 H), 8.65–8.75 (m, 6-pyr-H, 2 H).

Anal. Calcd for $C_{20}H_{15}NO$ (*Z*-**22**): C, 84.18; H, 5.30; N, 4.91. Found: C, 84.51; H, 5.18; N, 4.91.

Anal. Calcd for $C_{19}H_{14}N_2O$ (*Z*-**24**): C, 79.70; H, 4.93; N, 9.79. Found: C, 79.44; H, 4.75; N, 9.67.

Method F. Dicyclohexylamine Catalyst. Deoxybenzoin (1.96 g, 10.0 mmol) and 2-pyridinecarboxaldehyde (1.07 g, 10.0 mmol) in benzene (20 ml) were refluxed utilizing a Soxhlet extractor equipped with a calcium hydride filled thimble. While refluxing over 6 h, dicyclohexylamine (1.81 g, 10.0 mmol) was added slowly. Evaporation to dryness and trituation with ether gave 1.76 g (58%) of *erythro*-3-hydroxy-1,2-diphenyl-3-(2′-pyridyl)propanone (**27a**): mp 149.5–150.5 °C; NMR δ 3.50–4.38 (s, –OH, 1 H, exchangeable with D_2O), 5.24 (d, pyr-C**H**–, J = 5 Hz, 1 H), 5.59 (d, PhC**H**–, J = 5 Hz, 1 H), 6.90–7.56 (m, ArH, 11 H), 7.73–8.03 (*o*-BzH, 2 H), 8.38–8.60 (m, 6-pyr-H, 1 H); ir (Nujol) 3400–3000 (broad, OH), 1675 (C=O), 1600, 1294, 1062, and 705 cm^{-1}.

Anal. Calcd for $C_{20}H_{17}NO_2$: C, 79.18; H, 5.65; N, 4.62. Found: C, 79.25; H, 5.59; N, 4.58.

Column chromatography of the mother liquor on silica gel using cyclohexane–ethyl acetate (2:1) gave an additional 390 mg (13%) of the propanone **27a**, mp 145–148 °C, and 440 mg (14.5%) of the corresponding threo isomer (**27b**): mp ~130 °C; NMR δ 3.81–4.48 (s, –OH, 1 H), 5.18 (d, pyr-C**H**, J = 7.5 Hz, 1 H), 5.46 (d, PhC**H**, J = 7.5 Hz, 1 H), 6.69–7.52 (m, ArH, 11 H), 7.76–8.08 (m, *o*-BzH, 2 H), 8.34–8.57 (m, 6-pyr-H, 1 H). An analytical sample of the latter isomer could not be obtained.

Thermal Equilibration of 1-Phenyl-2-*N*-piperidino-2-(2′-pyridyl)benzoylethane (26). A benzene solution of **26** showed no change after 15 h at 85 °C; therefore, it was sealed in a tube and heated at 160 °C for 30 min. After cooling, the mixture was chromatographed on silica gel eluting with cyclohexane–ethyl acetate (4:1) to give predominantly starting material along with 116 mg (26%) of its stereoisomer: NMR δ 0.87–1.55 (m, 3,4,5-pip-H, 6 H), 1.73–2.93 (m, 2,6-pip-H, 4 H), 4.66 (d, pyr-C**H**, J = 10.5 Hz, 1 H), 5.83 (d, PhC**H**, J = 10.5 Hz, 1 H), 6.70–7.62 (m, ArH, 11 H), 7.77–8.11 (m, *o*-BzH, 2 H), 8.45–8.63 (m, 6-pyr-H, 1 H). Attempted purification of this isomer was not successful.

Condensation of 2-(4′-nitrophenyl)acetophenone with benzaldehyde followed the above general procedure via method E, except that crude benzaldehyde, which contained several percent of benzoic acid, was utilized. The theoretical amount of water was collected within 1 h. Reflux was continued for an additional 1 h, then the mixture was cooled and concentrated. The residue was recrystallized from benzene–cyclohexane to afford a mixture of both isomers. Separation of the low-melting *Z* isomer was easily achieved by recrystallization from 95% ethanol affording 2.1 g (25%) of *Z*-**23**: NMR δ 7.0–7.78 (m, ArH and vinyl H, 11 H), 7.86–8.35 (m, *o*-BzH and 3′,5′-ArH, 4 H); other spectral data are in Table II.

The mother liquor afforded 5.1 g (62%) of the *E* isomer: NMR δ 6.85–7.35 (m, ArH and vinyl H, 11 H), 7.35–8.10 (*o*-BzH, 2 H), 8.10–8.45 (m, 3′,5′-ArH, 2 H); other spectral data are in Table II.

General Photoisomerization of Substituted Benzoylethenes and Ethyl Acrylates. A 0.01 M benzene solution of either *Z*-**20**, *Z*-**22**, or *Z*-**24** was flushed well with argon and allowed to stand in direct sunlight for 4–6 h. Evaporation of the solvent and chromatography (THLC) gave 25–35% of the corresponding *E* isomer, with the exception of **20** whose isomers were inseparable under the chromatography conditions: *E*-**22** [NMR δ 6.4–7.75 (m, ArH, vinyl H, 12 H), 7.75–8.11 (m, *o*-BzH, 2 H), 8.55–8.84 (m, 6-pyr-H, 1 H)]; *E*-**24** [NMR δ 6.79–7.82 (m, ArH and vinyl H, 10 H), 7.82–8.13 (m, *o*-BzH, 2 H), 8.44–8.74 (m, 6-pyr-H, 2 H)]; other selected spectral and physical data are given in Table II.

This general procedure was conveniently applied to the ethyl acrylates. When a 4.5 × 10^{-3} M benzene solution of ethyl (*Z*)-2,3-di(2′-pyridyl)acrylate (**14**) was subjected to direct sunlight under an inert atmosphere for 4 days, after concentration, the residue was chromatographed (THLC) affording (88%) ethyl (*E*)-2,3-di(2′-pyridyl)acrylate, bp 129–132 °C (0.6 mm).

Prolonged exposure times increases the amount of *E* isomer; the reaction conditions were not optimized.

Acknowledgments. The authors gratefully acknowledge partial support of this work by the Public Health Service grant from the National Institutes of Health (GM-20985-04A2) and the National Science Foundation (GP-42816).

Registry No.—**8**, 100-52-7; **10**, 1121-60-4; **15**, 451-40-1; **16**, 3769-82-2; **17**, 1620-53-7; **18**, 555-16-8; *erythro*-**26**, 59169-61-8; *threo*-**26**, 59169-62-9; **27a**, 59169-63-0; **27b**, 59169-64-1; ethyl 2-pyridylacetate, 2739-98-2; ethyl phenylacetate, 101-97-3; (*E*)-2-phenylcinnamic acid, 91-48-5; (*Z*)-2-phenylcinnamic acid, 91-47-4; deoxybenzoin, 451-40-1; piperidine, 110-89-4.

References and Notes

(1) (a) Previous paper in this series: G. R. Newkome, N. B. Islam, and J. M. Robinson, *J. Org. Chem.*, **40**, 3514 (1975). (b) Presented in part at the 163rd National Meeting of the American Chemical Society, Boston, Mass., April 1972, Abstract No. ORGN-145. (c) Based in part on the Ph.D. Dissertation of J. M. R., Louisiana State University (Baton Rouge), 1973. Grateful acknowledgment is made to the Dr. Charles E. Coates Memorial Fund of the LSU Foundation for financial aid toward the preparation of this dissertation.
(2) (a) W. Jenney and H. Holzrichter, *Chemia*, **22**, 306 (1968); **23**, 158 (1969); also see (b) W. Baker, K. M. Buggle, J. F. W. McOmie, and D. A. M. Watkins, *J. Chem. Soc.*, 3594 (1958); (c) T. Kauffmann, G. Beissner, W. Sahm, and A. Woltermann, *Angew. Chem. Int. Ed. Engl.*, **9**, 808 (1970); (d) H. J. J-B. Martel and M. Rasmussen, *Tetrahedron Lett.*, 3843 (1971); (3) K. Galusko, *Rocz. Chem.*, **49**, 1597 (1975).
(3) V. Boekelheide and J. A. Lawson, *Chem. Commun.*, 1558 (1970).
(4) G. R. Newkome and D. L. Koppersmith, *J. Org. Chem.*, **38**, 4461 (1973).
(5) (a) J. L. R. Williams, R. E. Adel, J. M. Carlson, G. A. Reynolds, D. G. Borden, and J. A. Ford, Jr., *J. Org. Chem.*, **28**, 387 (1963); (b) S. Miyano and N. Abe, *Chem. Pharm. Bull.*, **15**, 511 (1967); (c) B. D. Shaw and E. A. Wagstaff, *J. Chem. Soc.*, 77 (1933); (d) J. Stanek and M. Horak, *Collect. Czech. Chem. Commun.*, **15**, 1037 (1950); (e) P. L. Kumler and R. A. Dybas, *J. Org. Chem.*, **35**, 125 (1970).
(6) (a) H. E. Zimmermann and L. Ahramjian, *J. Am. Chem. Soc.*, **81**, 2086 (1959); (b) R. Ketcham, *J. Chem. Educ.*, **41**, 565 (1964); R. Ketcham and D. J. Jambotkar, *J. Org. Chem.*, **28**, 1034 (1963).
(7) (a) W. B. Black and R. E. Lutz, *J. Am. Chem. Soc.*, **75**, 5990 (1953); (b) C. L. Schilling, Jr., and J. F. Mulvaney, *J. Org. Chem.*, **32**, 1673 (1967); (c) B. J. Kurtov and C. G. Kratchanov, *J. Chem. Soc. B*, 649 (1969).
(8) G. R. Newkome, J. M. Robinson, and N. S. Bhacca, *J. Org. Chem.*, **38**, 2234 (1973).
(9) D. R. Bragg and D. G. Wibberley, *J. Chem. Soc.*, 5074 (1961).
(10) I. Shahak, *J. Chem. Soc.*, 3160 (1961).
(11) J. R. Johnson, *Org. React.*, **1**, 210 (1942).
(12) L. Fieser, "Experiments in Organic Chemistry", 2d ed, Raytheon Education Co., Lexington, Mass., 1969, p 230.
(13) V. R. Valente and J. L. Wolfhagen, *J. Org. Chem.*, **31**, 2508 (1966), and references cited therein.
(14) R. H. Mills, M. W. Farrar, and P. J. Weinkauff, *Chem. Ind. (London)*, 2144 (1962).
(15) E. P. Kohler and E. M. Nygaard, *J. Am. Chem. Soc.*, **52**, 4128 (1930).
(16) A. Fischer, B. A. Grigor, J. Packer, and J. Vaughan, *J. Am. Chem. Soc.*, **83**, 4208 (1961).
(17) N. Goldberg, L. Barkley, and R. Levine, *J. Am. Chem. Soc.*, **73**, 4301 (1951).
(18) P. J. Duke and D. W. Boykin, Jr., *J. Org. Chem.*, **37**, 1436 (1972).
(19) M. Segers and A. Bruylants, *Bull. Soc. Chim. Belg.*, **64**, 87 (1955); *Chem. Abstr.*, **50**, 4869*f* (1956).
(20) J. L. R. Williams, S. K. Webster, and J. A. Van Allan, *J. Org. Chem.*, **26**, 4893 (1961); C. E. Loader, M. J. Sargent, and C. J. Timmons, *Chem. Commun.*, 127 (1965); H.-H. Perkampus and G. Kassebeer, *Justus Liebigs Ann. Chem.*, **696**, 1 (1966); R. H. Martin and M. Deblecker, *Tetrahedron Lett.*, 3597 (1969); G. Cauzzo, G. Galiazzo, P. Bortolus, and F. Coletta, *Photochem. Photobiol.*, **13**, 445 (1971); D. G. Witten and Y. J. Lee, *J. Am. Chem. Soc.*, **94**, 9142 (1972).
(21) G. R. Newkome, N. B. Islam, and J. M. Robinson, *J. Org. Chem.*, **40**, 3514 (1975).

(22) R. N. Castle and W. S. Seese, J. Org. Chem., 20, 987 (1955); G. N. Walker, J. Med. Chem., 8, 583 (1965).
(23) In CCl_4, this isomeric differentiation was not possible.
(24) F. Coletta, A. Gambaro, and L. Pasimeni, Gazz. Chim. Ital., 103, 265 (1973).
(25) J. H. Schauble, G. J. Walter, and J. G. Morin, J. Org. Chem., 39, 755 (1974).
(26) L. E. Friedrich and R. A. Cormier, J. Org. Chem., 35, 450 (1972).
(27) C. G. Kratchanov, Ts. D. Obretenov, and B. J. Kurtev, Synthesis, 263 (1972).
(28) S. Spasov, Tetrahedron, 25, 3631 (1969).

Studies on the Syntheses of Heterocyclic Compounds. 657.[1a] Total Synthesis of Angustine, Naucléfine, and Gentianine[1b]

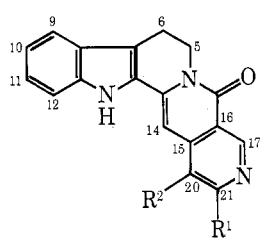
Tetsuji Kametani,* Mitsuhiro Takeshita, Masataka Ihara, and Keiichiro Fukumoto

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai, Japan

Received January 16, 1976

Condensation of 4-methyl-5-vinylnicotinonitrile (**7**) with ethyl oxalate, followed by acid hydrolysis, gave 3-ethoxycarbonyl-1-oxo-5-vinylpyrano[4,3-*c*]pyridine (**10**), which was heated in wet dimethylformamide to afford an unexpected product, gentianine (**6**). Gentianine (**6**) was also prepared directly from **7**. Condensation of **7** with ethyl formate yielded 3,4-dehydrogentianine (**16**). Treatment of the lactone (**10**) with tryptamine gave the 7-azaisocarbostyril (**14**), from which angustine (**1**) was synthesized by direct acid treatment or basic hydrolysis, followed by acidic cyclization. By the reaction of 3,4-dehydrogentianine (**16**) with tryptamine in acidic conditions, angustine (**1**) was also synthesized and naucléfine (**4**) was synthesized from nicotinonitrile (**17**) in a similar way.

In 1973, Cheng and his co-workers reported the isolation of angustine (**1**), angustoline (**2**), and angustidine (**3**) from *Strychnos angustiflora*.[2] Since then their distribution in species of *Mitragyna, Naucléa, Uncaria,* and *Strychnos* has been established.[3] Recently the related bases naucléfine (**4**) and nauclétine (**5**) were found in *Naucléa latifolia*.[4] Their

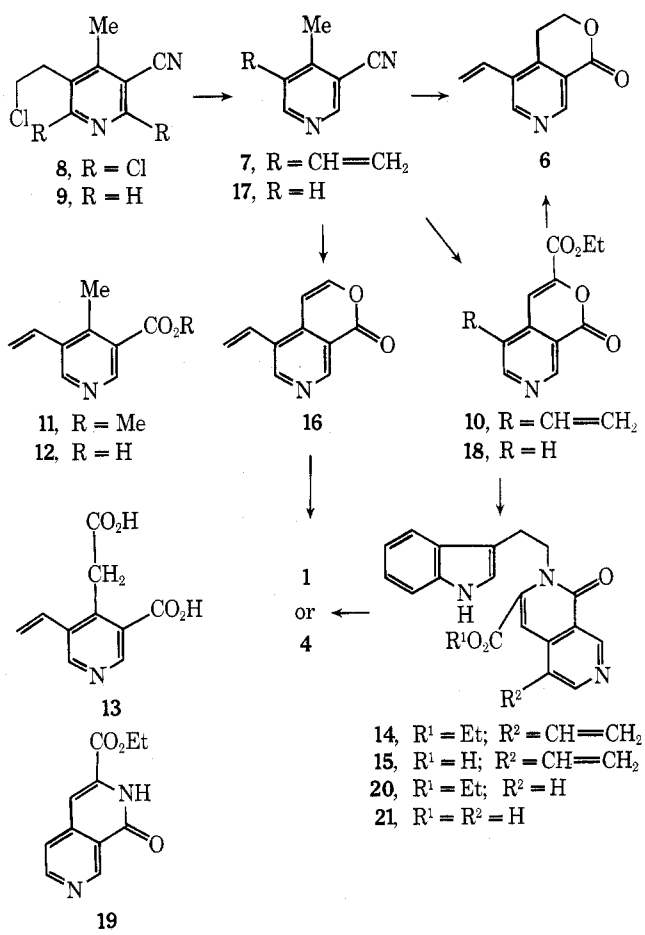


1, $R^1 = H$; $R^2 = -CH(19)=CH_2(18)$
2, $R^1 = H$; $R^2 = -CH(OH)Me$
3, $R^1 = Me$; $R^2 = H$
4, $R^1 = R^2 = H$
5, $R^1 = H$; $R^2 = COMe$

structures were assigned on the basis of spectral evidences and confirmed by the synthesis of angustoline (**2**),[5] angustidine (**3**),[6,7] and naucléfine (**4**).[4] Angustoline had been already converted into angustine (**1**).[2] It seemed worthwhile from a pharmacological point of view to investigate an effective synthesis of angustine and its derivatives. They are essentially *corynanthé* type alkaloids incorporating in their skeleton a tryptamine moiety and a secologanin monoterpene unit closely related to the alkaloid, gentianine (**6**).[2] We had therefore planned their synthesis using gentianine-like compounds and herewith describe biomimetic total syntheses of angustine (**1**) and naucléfine (**4**), and an alternative synthesis of gentianine (**6**).

According to a modified Govindachari procedure,[8] 4-methyl-5-vinylnicotinonitrile (**7**) was prepared via 2,6-dichloro-5-(2-chloroethyl)-3-cyano-4-methylpyridine (**8**) and 5-(2-chloroethyl)-4-methylnicotinonitrile (**9**). The nitrile **7** was condensed with ethyl oxalate in the presence of sodium hydride in benzene and in situ treated with diluted hydrochloric acid[9] to give the lactone **10**, mp 120 °C, in 76% yield.

Krapcho and Lovey had already carried out the decarboxylation of geminal diesters, β-keto esters, and α-cyano esters by heating in the presence of sodium chloride in wet dimethyl sulfoxide or wet dimethylformamide.[10] It was furthermore reported that even in the absence of sodium chloride, the reaction proceeded satisfactorily.[11,12] In expectation of a decarboxylation, the lactone **10** was heated with sodium chloride in wet dimethylformamide for 3 days and an unexpected product, mp 80–81 °C, *m/e* 175 (M^+), was isolated in 12% yield



after purification by column chromatography. The ir spectrum (in potassium bromide) of the product showed a carbonyl absorption at 1720 cm^{-1} and the NMR spectrum (δ in deuteriochloroform) revealed two neighboring methylene groups at 3.09 and 4.55 (each 2 H, each t, J = 6 Hz), a vinyl group at 5.59 (1 H, dd, J = 2 and 11.5 Hz), 5.76 (1 H, dd, J = 2 and 18 Hz), and 6.80 (1 H, dd, J = 11.5 and 18 Hz), and two aromatic protons at 8.80 and 9.11 ppm (each 1 H, each s). These spectral data suggested the product to be gentianine (**6**), which was also confirmed by direct comparison with an authentic sample.