There is strong evidence for interactions between N_3^- and substrate in these pyridinium ion reactions, and submicellar aggregates are probably involved. It is difficult to obtain pysical evidence on these systems, in part because of the high reaction rates but also because techniques such as light scattering are unsatisfactory for such dilute solutions. There is a similar problem for reactions in nonmicellizing hydrophobic ammonium ions where formation of small aggregates is assumed,[22,23] although the aggregates have not been detected by physical measurement.

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A Study and Mechanistic Interpretation of the Electronic and Steric Effects That Determine the Stereochemical Outcome of the Reaction of Schiff Bases with Homophthalic Anhydride and 3-Phenylsuccinic Anhydride

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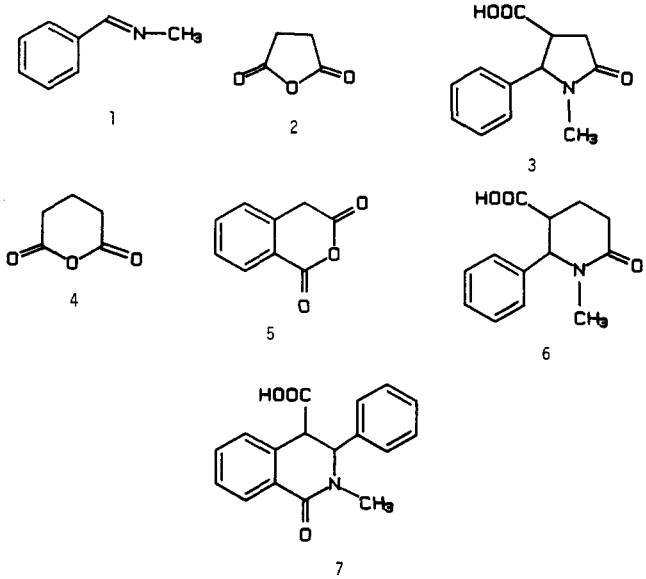
A study has been undertaken of the electronic and steric effects that determine the ratios of *cis*- and *trans*-isoquinolones **9** formed in the condensation of para-substituted Schiff bases **8** with homophthalic anhydride (**5**). A linear correlation between the ratios of the *cis*- and *trans*-isoquinolones formed and the Hammett σ^+ constants of the substituents in the aromatic ring has been observed. Electron-donating substituents have been found to favor formation of the cis diastereomers, while electron-attracting substituents result in the production of greater amounts of the trans diastereomers. In addition, it has been found that bulky substituents on the nitrogen atom of the Schiff bases result in the exclusive formation of the cis diastereomers. A mechanistic interpretation of these results has been proposed involving iminolysis of the anhydride as the initial event in which the *E* imines give rise to *cis*-isoquinolones and the *Z* imines result in formation of the trans diastereomers. The linear Hammett relationship observed between the ratios of diastereomers formed and the σ^+ values of substituents in the para position of the imines **8** means that there is a higher carbocationic character in the transition state of the rate-limiting step leading to the cis product than that leading to the trans product. This indicates that the rate-limiting step in the production of the cis diastereomer is probably the initial iminolysis of the anhydride **5**, while the rate-limiting step in production of the trans isomer is likely the *E*-*Z* isomerization of the Schiff base. Similar, although weaker, trends were observed in reactions involving 3-phenylsuccinic anhydride (**18**).

Since the discovery of the condensation of benzylidenemethylamine (**1**) with succinic anhydride (**2**) to form



substituted 2-pyrrolidinones **3**,[1] the reaction has been extended to glutaric[2] and homophthalic anhydrides (**4**, **5**), resulting in piperidinones and isoquinolones of general structures **6** and **7**, respectively. The latter reaction has been utilized in the preparation of a variety of protoberberine,[3] benzophenanthridine,[4] and B-secoprotoberberine[5] alkaloids as well as certain indenoisoquinolines possessing significant antitumor activity.[6] These reactions along with several related condensations have recently been reviewed.[7]

The reaction products resulting from these condensations possess two asymmetric centers and are therefore capable of existing as cis and trans diastereomers. Although an empirical relationship between solvent polarities

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Table I. Trans/Cis Ratios of Products 9 Obtained in the Condensation of Schiff Bases 8 with Homophthalic Anhydride (5)

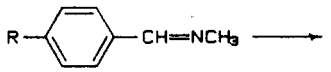
R (σ^+)[a]	in $CHCl_3$[b]	in MeOH	in $HCONH_2$
NO_2 (0.74)	97/3	72/28	63/37
Cl (0.04)	82/18	61/39	61/39
H (0)	83/17	64/36	61/39
CH_3 (−0.25)	75/25	63/37	58/42
OCH_3 (−0.65)	69/31	60/40	55/45
$N(CH_3)_2$ (−1.5)	20/80	45/55	53/47

[a] The σ^+ values in Tables I and II were taken from ref 8, except that for *N,N*-dimethylamino, which was obtained from ref 9.

and the ratios of diastereomers formed has been recognized in the condensation of certain Schiff bases and homophthalic anhydrides,[4f] the factors that determine the stereochemical outcomes of these reactions have remained unknown, so that predictions about which diastereomer would be predominantly formed in a specific reaction have not previously been possible. We have therefore undertaken a detailed study of the electronic and steric factors that influence the stereochemical outcome of the reaction of a variety of Schiff bases with homophthalic anhydride and 3-phenylsuccinic anhydride (**18**), and we have attempted to rationalize these effects in mechanistic terms.

Results

The reaction of para-substituted imines **8** with homophthalic anhydride (**5**) was performed in three different solvents, and the influence of the substituents on the ratios of isomers *trans*-**9** and *cis*-**9** formed was estimated by



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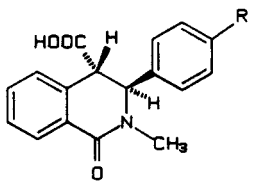
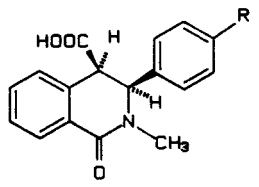


trans-9



cis-9

a, R=NO_2 d, R=CH_3
b, R=Cl e, R=OCH_3
c, R=H f, R=$N(CH_3)_2$

NMR integration of the signals corresponding to the C-3 methine hydrogens, which appeared near δ 5. The coupling constants J_{AB} were 1 Hz for the trans diastereomers, in which the phenyl and carboxyl substituents are pseudoaxial, and 6 Hz for the cis isomers, in which the phenyl group is pseudoaxial and the carboxyl group is pseudoequatorial.[3a] The product ratios are listed in Table I.

Linear Hammett plots were obtained from these data by plotting

$$\log\left[\frac{\%\ trans\text{-}9\text{-}R/\%\ cis\text{-}9\text{-}R}{\%\ trans\text{-}9\text{-}H/\%\ cis\text{-}9\text{-}H}\right] \text{ vs. } \sigma^+$$

where 9-R and 9-H represent para-substituted and para-unsubstituted Schiff bases. Table II gives the calculated values for the logarithmic term above.

Figure 1 is a Hammett plot of the data list in Table II. In Table III, the calculated ρ values for the condensation reaction in chloroform, methanol, and formamide are listed, along with the y intercepts and correlation coefficients (R). The correlations revealed in this study are as

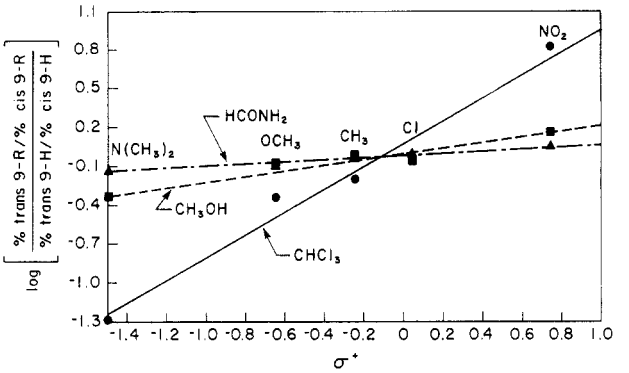


Figure 1. Hammett plots of the data listed in Table II.

Table II. log (% *trans*-9-R/% *cis*-9-R)/(% *trans*-9-H/% *cis*-9-H) for Data Listed in Table I

R (σ^+)	in $CHCl_3$	in MeOH	in $HCONH_2$
NO_2 (0.74)	0.821	0.160	0.0369
Cl (0.04)	−0.030	−0.056	0.00
H (0)	0	0	0
CH_3 (−0.25)	−0.212	−0.0187	−0.054
OCH_3 (−0.65)	−0.341	−0.0738	−0.107
$N(CH_3)_2$ (−1.50)	−1.290	−0.337	−0.142

Table III. Calculated σ Values for the Imine-Anhydride Condensation Reaction

	in $CHCl_3$	in MeOH	in $HCONH_2$
slope (ρ)	0.890	0.206	0.088
y intercept	0.066	0.0017	−0.020
correln coeff (R)	0.986	0.962	0.961

good as can be expected given the limitations of NMR integrations, which are only accurate within a few percent, and the values of the Hammett σ^+ constants, which are themselves subject to experimental error.[10]

A separate series of reactions involved competition experiments in which imine **8c** was allowed to compete with imines **10a–c** for reaction with homophthalic anhydride

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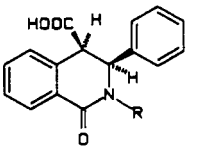

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a, R=cyclo-C_6H_{11}
b, R=tert-C_4H_9
c, R=C_6H_5
d, R=$CH_2CH(CH_3)_2$
e, R=CH_2CH_3
f, R=$CH(CH_3)_2$

(**5**) according to the general equation

5 + 8 equiv of imine **8c** + 8 equiv of imines **10a–c** → products

A steric effect of considerable magnitude was realized in the observation that **9c** was the *exclusive* reaction product of all competition experiments involving imine **8c**. A further result regarding electronic effects was obtained when it was found that the bulky *tert*-butylimine **10b** reacted preferentially over the less hindered, but also less nucleophilic *N*-benzalaniline (**10c**).

The steric bulk of the N substituent of the imine also has an effect on the ratios of diastereomers formed.

(10) For example, compare the numbers given in ref 8 with those appearing in: March, J. *Advanced Organic Chemistry*, 2nd ed.; McGraw-Hill, New York, 1977; p 253.

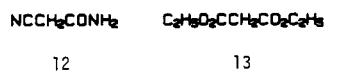
Table IV. Trans/Cis Ratios of Products 19 Obtained in the Condensation of Schiff Bases 8 with Phenylsuccinic Anhydride (18)

R (σ^+)	in $CHCl_3$	R (σ^+)	in $CHCl_3$
Cl[a] (0.04)	77/23	OCH_3 (−0.65)	75/25
H (0)	82/18	$N(CH_3)_2$ (−1.5)	68/32
CH_3 (−0.25)	77/23		

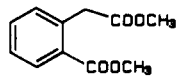
[a] The initially formed carboxylic acids were isolated as their methyl esters.

Whereas the *N*-methyl-substituted imines predictably reacted with homophthalic anhydride (**5**) to afford mixtures of cis and trans diastereomers, only the cis isomes **11a–d** were isolated from reaction mixtures involving the Schiff bases **10a–d** having larger substituents on the nitrogen. As expected, the sterically hindered Schiff bases **10a–d** were also less reactive and required longer reaction times than imines **8a–e**. In addition, the yields of products **11a–d** were moderate in comparison to those obtained from the sterically less hindered imines **8a–e**.

Several experiments were also run in which active methylene compounds were incubated with benzylidenemethylamine (**8c**) in $CDCl_3$ under conditions resulting in reaction of homophthalic anhydride (**5**) with **8c**. Compounds **12** and **13** were unreactive at room temperature,



12 13



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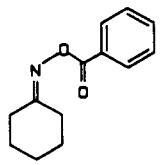

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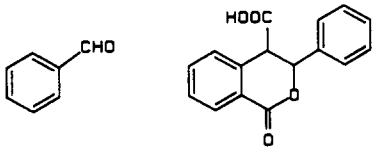
while dimethyl homophthalate (**14**) did not react even when heated at reflux in $CDCl_3$ for 20 h. The oxime ester **15** was also found to be unreactive when exposed to homophthalic anhydride.

A competition experiment was run in which Schiff base **8c** was allowed to compete with benzaldehyde **16** for reaction with homophthalic anhydride in the presence of triethylamine. The mixture of isoquinolones **9** was formed predominantly. Lactone **17** was a minor product in this reaction.



16 17

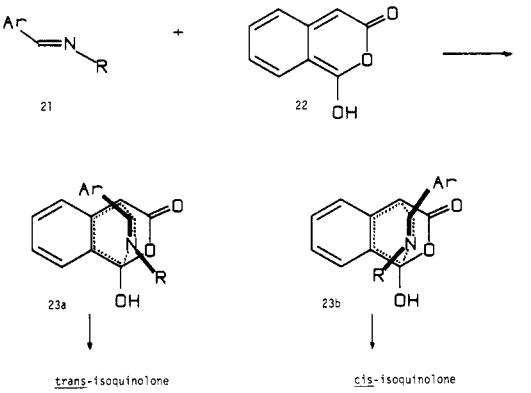
The electronic and steric determinants of the stereochemical outcome of the reaction were also probed with use of phenylsuccinic anhydride (**18**). The results involving the series of para-substituted benzylidenemethylamines are listed in Table IV. The results showing the effect of varying the N substituent in a series of benzylidenealkylamines are displayed in Table V. In summary, the reactions involving phenylsuccinic anhydride (**18**) show the same general trends regarding the electronic and steric effects on the stereochemical outcome of the condensation reaction as those involving homophthalic anhydride (**7**), but these effects are weaker with phenylsuccinic anhydride than with homophthalic anhydride. Phenylsuccinic anhydride (**18**) was found to be less reactive than homophthalic anhydride (**7**), and the reactions involving phenylsuccinic anhydride listed in Table IV do not show the same linear correlation with the Hammett σ^+ values of the para substituents of the imine as do those involving homophthalic anhydride.

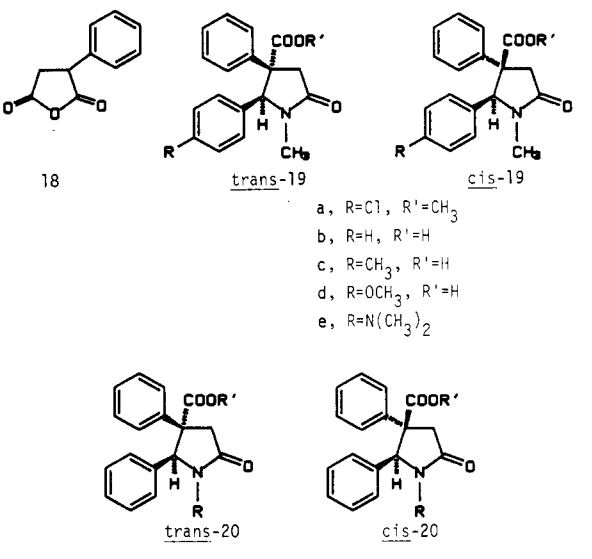
Table V. Trans/Cis Ratios of Products 20 Obtained in the Condensation of Schiff Bases 10e, 10f, and 10b with Phenylsuccinic Anhydride (18)

imine	product	N subst (R)	trans/cis (in $CHCl_3$)
10e	**20a**[a]	CH_2CH_3	86/14
10f	**20b**[a]	$CH(CH_3)_2$	60/40
10b	**20c**	$C(CH_3)_3$	32/68

[a] The initially formed carboxylic acids were isolated as their methyl esters.

Scheme I





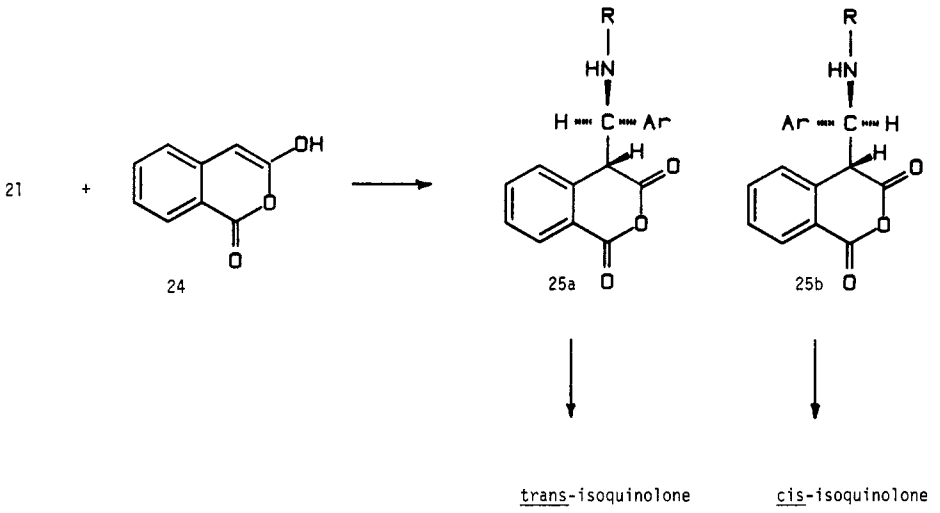
a, R=Cl, R'=CH_3
b, R=H, R'=H
c, R=CH_3, R'=H
d, R=OCH_3, R'=H
e, R=$N(CH_3)_2$

a, R=CH_2CH_3, R'=CH_3
b, R=$CH(CH_3)_2$, R'=CH_3
c, R=$C(CH_3)_3$, R'=H

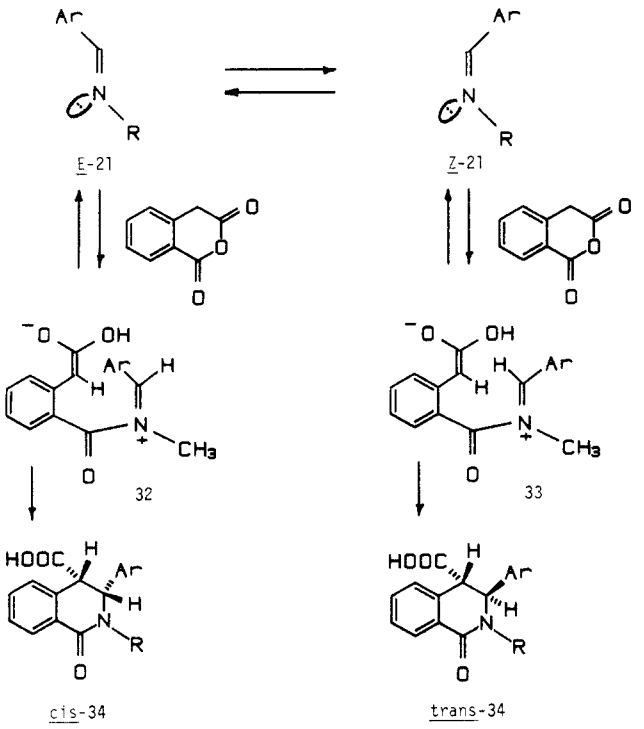
Discussion

Three mechanisms have been considered in an attempt to rationalize the correlation of the stereochemical outcome of the condensation of Schiff bases with homophthalic anhydride (**5**). The first of these invokes an imino Diels–Alder reaction between the Schiff base **21** and the dienol tautomer **22** of homophthalic anhydride, which has been previously proposed as a reactant in the condensation of homophthalic anhydride and a variety of dienophiles[11] (Scheme I). However, in contrast to the known condensation of **22** with dienophiles, which requires prolonged

Scheme II

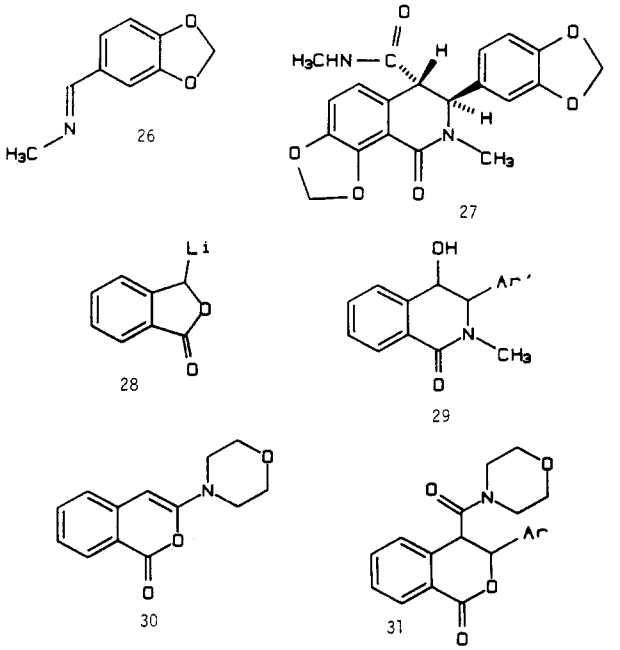


Scheme III



heating at 100–200 °C, the reaction of Schiff bases **21** with homophthalic anhydride proceeds exothermally at room temperature and is complete in a matter of seconds. One would expect that imines **21** would be *less* reactive than the very reactive dienophiles (e.g., dimethylacetylene dicarboxylate[11a]) that are reported to condense with homophthalic anhydride, since simple uncharged alkylimines are usually unreactive in the imino Diels–Alder reaction.[12] Although it is known that the reaction of homophthalic anhydride with dienophiles can be accelerated by deprotonation of the anhydride to form a dienolate anion,[13] the generation of the dienolate requires strong bases such as lithium diisopropylamide or sodium hydride. Use of weaker bases such as pyridine, triethylamine, potassium carbonate, and potassium hydroxide is ineffective.[13] It is therefore very unlikely that any dienolate anion could be involved in the condensation of Schiff bases with homophthalic anhydride. Examination of the two transition states **23a** and **23b** for the hypothetical imino Diels–Alder pathway leads to the conclusion that bulky substituents on the nitrogen would tend to favor **23a** over **23b**, thus leading preferentially to the formation of the trans reaction product. The opposite is in fact true. Bulky substituents favor production of the *cis*-isoquinolones. Another difficulty with a concerted mechanism is that, on the basis of other examples of imino Diels–Alder reactions,[12] one would expect *N*-benzalaniline (**10c**) to react more rapidly with homophthalic anhydride than the *tert*-butylimino **10b**, which is decidedly not the case. It is also known that oxime esters react readily with dienes to give normal Diels–Alder cycloadducts. However, *O*-benzoylcyclohexanone oxime (**15**) failed to react with homophthalic anhydride after prolonged heating in chloroform. For these reasons, the imino Diels–Alder pathway does not appear to be tenable.

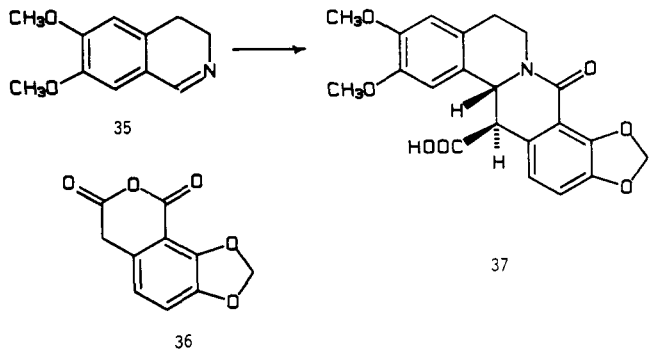
A second possible pathway views the reaction as proceeding as the nitrogen analogue of the Perkin reaction (Scheme II). In this case, C–C bond formation precedes C–N bond formation. Dimethyl homophthalate (**14**) has been condensed with piperonylidenemethylamine (**26**) in



(11) (a) Tamura, Y.; Wada, A.; Sasho, M.; Kita, Y. *Tetrahedron Lett.* **1981**, *22*, 4283. (b) Tamura, Y.; Wada, A.; Sasho, M.; Fukunaga, K.; Maeda, H.; Kita, Y. *J. Org. Chem.* **1982**, *47*, 4376.
(12) Weinreb, S. M.; Leven, J. I. *Heterocycles* **1979**, *12*, 949.
(13) Tamura, Y.; Sasho, M.; Nakagawa, K.; Tsugoshi, T.; Kita, Y. *J. Org. Chem.* **1984**, *49*, 473.

the presence of excess methylamine to yield the isoquinolone **27** in a reaction which almost certainly proceeds by a Perkin-type mechanism.[14] However, the conditions required (refluxing for 1 week in sodium methoxide–methanol solution) are drastically different from those employed for the homophthalic anhydride–Schiff base condensation. Dimethyl homophthalate (**14**) proved to be unreactive under the conditions of the homophthalic anhydride reactions, as were **12** and **13**. The results of the competition experiment in which imine **8c** was allowed to compete with benzaldehyde (**16**) for reaction with homophthalic anhydride in the presence of triethylamine also mitigate against a Perkin-type process for the imine–anhydride condensation, since one would expect on the basis of the greater electronegativity of oxygen vs. nitrogen that the aldehyde would be more reactive than the imine if both reactions were proceeding by the same Perkin-type mechanism. However, the opposite was observed, with the isoquinolones **9** being mainly formed at the expense of the lactone **17**. Implicit in this argument is the assumption that the neutral imine is reacting, since in the presence of triethylamine very little of the protonated iminium ion is present. In addition, it is difficult to rationalize the linear Hammett relationship shown in Figure 1 on the basis of the Perkin mechanism. Dodsworth et al. reported that in the condensation of a series of substituted Schiff bases with the lithium phthalide (**28**), in which C–C bond formation precedes C–N bond formation, a constant ratio of ca. 1:1.8 for the cis and trans isomers **29** was formed.[15a] If anything, electron-donating substituents in the para position of the Schiff base appear to slightly favor production of the trans isomer in that reaction,[15b] which is opposite to the trend observed in the homophthalic anhydride–imine condensation. The stereochemical outcome of the reaction of the morpholinobenzopyranone (**30**) with a series of para-substituted benzaldehydes to yield lactones **31**, in which C–C bond formation presumably precedes C–D bond formation, also does not appear to follow the stereochemical trend observed for the homophthalic anhydride–imine reaction.[16] It should also be pointed out that the Perkin mechanism was previously considered in the condensation of a series of imines with succinic anhydride (**2**) but was rejected in that case because the reaction was found to be accelerated by electron-donating substituents and retarded by electron-attracting substituents in the para position of the aldehyde-derived aromatic ring of the Schiff base, which is opposite to what would be expected for a Perkin-type mechanism.[1b]

The third possibility, which seems to be most consistent with the experimental observations, is outlined in Scheme III. According to this proposal, the *cis*-isoquinolone arises from iminolysis of the *E* Schiff base, while the *trans*-isoquinolone is formed from the corresponding reaction of the *Z* Schiff base. This would explain why Schiff bases having large substituents on nitrogen such as **10a** and **10b**, in which the form (*Z*)-**21** is highly unfavored due to nonbonded interactions between the R and Ar groups, yield only *cis*-isoquinolones. It also provides a rationale for the observation that the condensation of 3,4-dihydroisoquinolines with homophthalic anhydrides such as the reaction of **35** and **36** always yield exclusively the trans diastereomers as exemplified by **37**,[3e] since these 3,4-dihydroisoquinolones are rigid cis imines. Although it is well-known that simple aldimines exist almost completely (>99%) in the *Z* form,[17-20] at least *some* of the cis isomer is present at equilibrium. A pronounced acid catalysis of the *E*–*Z* isomerization of imines is also documented, and cases are known in which the half-life for this process has been decreased from 30 h to less than 1 min.[20,21] Sufficient amounts of (*Z*)-**21** could therefore be maintained in the imine–anhydride condensation reaction mixtures, since the products of the reaction are, after all, carboxylic acids. It is also expected that the *Z* Schiff base would be significantly more reactive with homophthalic anhydride than the *E* isomer, both because it is less stable and because reaction with the anhydride is less sterically hindered by the Ar group in (*Z*)-**21** than in (*E*)-**21**, so that significant amounts of *trans*-**34** are formed relative to *cis*-**34** even though the ratio of (*E*)-**21** to (*Z*)-**21** is large.



The pathway proposed in Scheme III also allows a rationale to be advanced for the relationship depicted in Figure 1 between the Hammett σ^+ values of substituents present in the para position of the aldehyde-derived aromatic ring of the Schiff bases and the stereochemical outcome of the condensation. This relationship may simply reflect the fact that the overall rates of the reactions resulting in production of *cis*-**34** have a different sensitivity to substituent effects than those resulting in formation of *trans*-**34**. The rate-limiting step in the production of *trans*-**34** from (*E*)-**21** could be isomerization of (*E*)-**21** to (*Z*)-**21** or the condensation of (*Z*)-**21** with the anhydride **5**. It is known that the rate of thermal imine isomerization is accelerated by electron-withdrawing substituents in the para position of the aldehyde-derived aromatic ring, and log *k* values for this process appear to correlate with the Hammett σ constants.[22] This would be consistent with the trends observed in Figure 1, assuming *E*–*Z* imine isomerization is rate limiting in production of *trans*-**34**. Thus, electron-donating substituents would decrease the rate of production of *trans*-**34** by increasing the activation energy for imine isomerization, while they would increase the rate of formation of *cis*-**34** by stabilizing the developing positive charge in the transition state leading to intermediate **32**. On the other hand, condensation of (*Z*)-**21** with anhydride **5** may determine the rate of production of *trans*-**34**, and the rate of the reaction involving (*E*)-**21** and **5** may be more sensitive to substituent effects than that of (*Z*)-**5**, which would also explain the relationship

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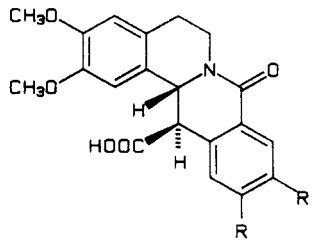
shown in Scheme I. It would be difficult to estimate the rate of isomerization of (*E*)-**21** to (*Z*)-**21** for the simple imines involved in this study because the latter are present in such low concentrations at equilibrium.

The iminolysis mechanism would also explain the previously described substituent effects on the rates of succinic anhydride (**2**) reactions, since electron-donating substituents in the para position of the aromatic ring should stabilize the positive charge developing during the iminolysis step.[1b]

It should be pointed out that there is some disagreement in the literature regarding the stereochemistry of the products derived from the condensation of Schiff bases with homophthalic anhydrides. Haimova et al. reported that the reaction of imines of type **21** yields *trans*-isoquinolones of general structure *trans*-**34**, while **35** was reported to condense with anhydrides related to **36** to yield cis-substituted protoberberines **38a** and **38b**.[23] These



38a, R=H
38b, R=OCH$_3$

results conflict with our own, which demonstrate that 3,4-dihydroisoquinolines always condense with homophthalic anhydrides to give trans-substituted protoberberines (e.g., **37**) as the kinetic products, which can be converted to the thermodynamically more stable cis isomers on heating in acetic acid.[3] However, Haimova et al. extracted their reaction mixtures with 10% aqueous NaOH during the isolation of the reaction products. We have found that 10% aqueous NaOH epimerizes the initially formed reaction products to the thermodynamically more stable isomers isolated by Haimova et al. If the products must be isolated by base extraction, which is usually not necessary, the epimerization can be avoided by using $NaHCO_3$ instead of NaOH.

Several other reports have also recently appeared in which the stereochemical outcome of reactions involving Schiff bases has been postulated to depend on imine geometry. These include the condensation of Schiff bases with cyanoketenes to form β-lactams[24] and the condensation of imines with lithium phthalides of general structure **28** to form isoquinolones related to **29**.[25] In addition, a correlation of the logs of the ratios of *cis*- and *trans*-diols formed in the acid-catalyzed hydrolysis of 1-arylcyclohexanones with the Hammett σ^+ constants of substituents in the aromatic ring has been reported by Berti et al.[26] Their treatment of the data is qualitatively similar to that utilized in the present study. It is interesting to note that, in the above-mentioned epoxide ring opening, electron-donating substituents also give more of the *cis*-diol and that the authors concluded on that basis that there is a higher degree of carbocationic character in the transition state leading to the cis product than that leading to the trans product. The same must also be true for the transition states of the rate-limiting steps of the reactions leading to *cis*-**34** and *trans*-**34**. Since it is difficult to imagine that the amount of carbocationic character in the transition states developed after iminolysis of the anhydride by (*E*)- and (*Z*)-**21** would be significantly different, the rate-limiting step in production of *trans*-**34** is probably *E*–*Z* imine isomerization.

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Experimental Section

Melting points were determined on a Thomas-Hoover Unimelt or on a Meltemp apparatus and are uncorrected. NMR spectra were recorded on a Varian FT-80 spectrometer in $CDCl_3$ solvent, except where noted. IR spectra were obtained on a Beckman IR-33 spectrophotometer. Microanalyses were performed by the Purdue Microanalytical Laboratory. The mass spectra were determined on a Finnigan 4000 spectrometer using an ionization potential of 70 eV. High-resolution mass spectra were determined on a Kratos MS50S spectrometer operating at 70 eV. Isoquinolones *cis*-**9c** and *trans*-**9c** were obtained as previously described.[3a]

***trans*-*N*-Methyl-3-(*p*-nitrophenyl)-4-carboxy-3,4-dihydro-1(2*H*)-isoquinolone (*trans*-9a).** Anhydride **5** (0.65 g, 4 mmol) was added to a solution of imine **8a** (0.66g, 4 mmol) in chloroform (5 mL). The reaction mixture was stirred at room temperature overnight, and the product was filtered: 1.14 g (87%); mp 231–234 °C dec; IR (KBr) 3400, 3020, 2910, 1715, 1640, 1510, 1340 cm^{-1}; NMR δ 8.15–7.22 (m, 8 H), 5.41 (d, 1 H, J = 1 Hz), 3.91 (d, 1 H, J = 1 Hz), 3.16 (s, 3 H); mass spectrum, m/e (relative intensity) 326 (M$^+$, 9), 297 (27), 165 (60), 163 (20), 162 (26), 160 (17), 134 (100), 118 (13), 117 (12), 105 (37), 91 (11), 90 (16), 89 (25), 77 (20), 76 (12). Anal. Calcd for $C_{17}H_{14}N_2O_5$: C, 62.57; H, 4.32; N, 8.58. Found: C, 62.56; H, 4.33; N, 8.81.

***trans*-*N*-Methyl-3-(*p*-chlorophenyl)-4-carboxy-3,4-dihydro-1(2*H*)-isoquinolone (*trans*-9b).** Anhydride **5** (1.07 g, 6.6 mmol) was added to a solution of imine **8b** (1.01 g, 6.6 mmol) in chloroform (10 mL), and the reaction mixture was stirred overnight at room temperature. The solvent was evaporated, and the solid was recrystallized from ethanol: 681 mg (33%); mp 114–116 °C; IR (KBr) 2900, 1720, 1690, 1640, 1615, 1480, 1390, 1250, 1080 cm^{-1}; NMR δ 8.19–6.93 (m, 8 H), 5.25 (d, 1 H, J = 1 Hz), 3.82 (d, 1 H, J = 1 Hz), 3.13 (s, 3 H); mass spectrum, m/e (relative intensity) 317 (M$^+$ + 2, 4), 315 (M$^+$, 16), 286 (19), 270 (25), 162 (21), 160 (16), 156 (28), 154 (93), 152 (35), 134 (100), 105 (42), 90 (12), 89 (31), 88 (13), 77 (25), 75 (19). Anal. Calcd for $C_{17}H_{14}NO_3Cl$: C, 64.67; H, 4.47; N, 4.44; Cl, 11.23. Found: C, 64.56; H, 4.43; N, 4.63; Cl, 11.31.

***cis*-*N*-Methyl-3-(*p*-chlorophenyl)-4-carboxy-3,4-dihydro-1(2*H*)-isoquinolone (*cis*-9b).** Anhydride **5** (0.53 g, 3.27 mmol) was added to a solution of imine **8b** (0.50 g, 3.25 mmol) in methanol (5 mL) at 40 °C, and the mixture was stirred for 2 min. The solution was then filtered, heated to boiling on the steam bath, and diluted with water (3.5 mL). The mixture was cooled slowly in a hot water bath heated initially to 80 °C. The resulting crystalline solid was filtered when the temperature of the bath had cooled to 40 °C: 0.25 g (24%); mp 192–194 °C; IR (KBr) 3020, 2540, 1740, 1710, 1640, 1590, 1570, 1480, 1390, 1260, 1250, 1230, 1160, 680 cm^{-1}; NMR δ 8.21–8.10 (m, 1 H), 7.58–7.38 (m, 3 H), 7.13 (d, 2 H, J = 9 Hz), 7.03 (d, 2 H, J = 9 Hz), 5.00 (d, 1 H, J = 6 Hz), 4.69 (d, 1 H, J = 6 Hz) 3.04 (s, 3 H); mass spectrum, m/e (relative intensity) 315 (M$^+$, 8), 162 (19), 156 (35), 154 (100), 134 (89), 105 (34), 89 (17), 77 (16). Anal. Calcd for $C_{17}H_{14}NO_3Cl$: C, 64.67; H, 4.47; N, 4.44; Cl, 11.23. Found: C, 64.46; H, 4.32; N, 4.36; Cl, 11.32.

***trans*-*N*-Methyl-3-(*p*-methylphenyl)-4-carboxy-3,4-dihydro-1(2*H*)-isoquinolone (*trans*-9d).** Anhydride **5** (1.18 g, 7.28 mmol) was added to a solution of imine **8d** (0.967 g, 7.26 mmol) in chloroform (10 mL), and the reaction mixture was stirred at room temperature for 1 h. The solvent was evaporated, and glacial acetic acid (10 mL) was added. The mixture was heated at reflux for 16 h. The acetic acid was evaporated, and the remaining solid was recrystallized from aqueous ethanol: 1.52 g (71%); mp 201–203 °C; IR (KBr) 2880, 1715, 1600, 1550, 1380, 1230, 1160, 1130 cm^{-1}; NMR δ 8.20–6.85 (m, 8 H), 5.17 (d, 1 H,

J = 1 Hz), 3.91 (d, 1 H, J = 1 Hz), 3.11 (s, 3 H), 2.25 (s, 3 H); mass spectrum, m/e (relative intensity) 295 (M^+, 11), 250 (10), 134 (100), 132 (20), 105 (22), 91 (12), 89 (17), 77 (13). Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.03; H, 5.82; N, 4.61.

***cis*-*N*-Methyl-3-(*p*-methylphenyl)-4-carboxy-3,4-dihydro-1(2*H*)-isoquinolone (*cis*-9d).** Anhydride **5** (0.61 g, 3.76 mmol) was added to a solution of imine **8d** (0.50 g, 3.75 mmol) in methanol (5 mL) at 40 °C. The mixture was stirred for 2 min and then filtered while hot. The solution was then heated on a hot water bath at 80 °C and diluted with water (5 mL). The mixture was allowed to stand for several hours at room temperature before filtration of the product as small white needles: 0.13 g (12%); mp 185–186 °C; IR (KBr) 3000, 1735, 1620, 1590, 1560, 1155 cm^{-1}; NMR δ 8.27–6.94 (m, 8 H), 4.94 (d, 1 H, J = 6 Hz), 4.73 (d, 1 H, J = 6 Hz), 3.05 (s, 3 H), 2.25 (s, 3 H); mass spectrum, m/e (relative intensity) 295 (M^+, 4), 134 (100), 133 (14), 105 (19), 89 (11), 85 (35), 83 (60). Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.36; H, 5.80; N, 4.44.

***trans*-*N*-Methyl-3-(*p*-methoxyphenyl)-4-carboxy-3,4-dihydro-1(2*H*)-isoquinolone (*trans*-9e).** Anhydride **5** (1.09 g, 6.72 mmol) was added to a solution of imine **8e** (1.01 g, 6.75 mmol) in chloroform (10 mL), and the mixture was stirred at room temperature for 1 h. The solvent was then evaporated and replaced by glacial acetic acid (10 mL). The mixture was heated at reflux for 20 h. The acetic acid was evaporated and the solid recrystallized twice from aqueous ethanol to yield white crystals: 1.14 g (55%); mp 190–193 °C; IR (KBr) 2940, 2900, 1690, 1630, 1590, 1500, 1250, 1230, 1160 cm^{-1}; NMR δ 8.20–6.68 (m, 8 H), 5.21 (d, 1 H, J = 1 Hz), 3.83 (d, 1 H, J = 1 Hz), 3.72 (s, 3 H), 3.12 (s, 3 H); mass spectrum, m/e (relative intensity) 311 (M^+, 22), 266 (11), 262 (13), 162 (8), 150 (100), 148 (44), 134 (63), 105 (30), 89 (17), 77 (19). Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.38; H, 5.42; N, 4.52.

***cis*-*N*-Methyl-3-(*p*-methoxyphenyl)-4-carboxy-3,4-dihydro-1(2*H*)-isoquinolone (*cis*-9e).** Anhydride **5** (0.54 g, 3.33 mmol) was added a solution of imine **8e** (0.50 g, 3.35 mmol) in methanol (5 mL) at 40 °C. After 2 min, the solution was filtered, heated to boiling on the steam bath, and diluted with water (5 mL). The flask was immersed in a water bath heated to 80 °C and allowed to cool slowly to 40 °C. A mixture of oil and solid precipitated. The mixture was reheated to 80 °C and the solid filtered at that temperature: 0.27 g (26%); mp 182–184 °C; IR (KBr) 3040, 1730, 1620, 1590, 1560, 1495, 1280, 1240, 1160, 815 cm^{-1}; NMR δ 8.25–8.15 (m, 1 H), 7.64–7.37 (m, 3 H), 6.99 (d, 2 H, J = 9 Hz), 6.60 (d, 2 H, J = 9 Hz), 4.95 (d, 1 H, J = 6 Hz), 4.68 (d, 1 H, J = 6 Hz), 3.70 (s, 3 H), 3.05 (s, 3H); mass spectrum, m/e (relative intensity) 311 (M^+, 21), 151 (11), 150 (100), 149 (21), 148 (37), 134 (51), 133 (10), 105 (30), 89 (13), 77 (15). Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.28; H, 5.48; N, 4.53.

***cis*-*N*-Methyl-3-[*p*-(dimethylamino)phenyl]-4-carboxy-3,4-dihydro-1(2*H*)-isoquinolone (*cis*-9f).** Anhydride **5** (715 mg, 4.41 mmol) was added to a solution of imine **8f** (715 mg, 4.41 mmol) in chloroform (20 mL). After 1 h at room temperature, the reaction mixture was cooled to 0 °C and the solid product was filtered: 737 mg (52%); mp 209–211 °C; IR (KBr) 3000, 2900, 1730, 1615, 1510, 1155 cm^{-1}; NMR δ 8.19–7.33 (m, 4 H), 6.68 (d, 2 H, J = 9 Hz), 6.49 (d, 2 H, J = 9 Hz), 4.90 (d, 1 H, J = 6 Hz), 4.65 (d, 1 H, J = 6 Hz), 3.05 (s, 3 H), 2.85 (s, 6 H); mass spectrum, m/e (relative intensity) 324 (M^+, 52), 280 (14), 163 (18), 162 (100), 161 (63), 146 (10), 134 (24), 121 (11), 118 (12), 105 (18), 77 (12). Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.62; H, 6.10; N, 8.62.

***cis*-*N*-Cyclohexyl-3-phenyl-4-carboxy-3,4-dihydro-1-(2*H*)-isoquinolone (*cis*-11a).** Anhydride **5** (865 mg, 5.33 mmol) was added to a solution of imine **10a** (1.00 g, 5.34 mmol) in chloroform (20 mL) at room temperature. After the mixture was stirred overnight, the solvent was evaporated and the resulting oil was recrystallized from aqueous methanol. The analytical sample was recrystallized twice from methanol: 1.24 g (67%); mp 184–188 °C; IR (KBr) 3060, 3020, 2920, 2840, 1740, 1710, 1615, 1590, 1560, 1460, 1430, 1200, 1160, 1140 cm^{-1}; NMR δ 8.25–6.99 (m, 9 H), 5.21 (d, 1 H, J = 6 Hz), 4.57 (d, 1 H, J = 6 Hz), 0.6–0.2 (m, 11 H); chemical ionization mass spectrum, m/e (relative intensity) 359 (M^+ + 1, 100), 188 (12). Anal. Calcd for $C_{22}H_{23}NO_3$: C, 75.62; H, 6.63; N, 4.01. Found: C, 75.58; H, 6.89; N, 3.75.

***cis*-*N*-*tert*-Butyl-3-phenyl-4-carboxy-3,4-dihydro-1-(2*H*)-isoquinolone (*cis*-11b).** Anhydride **5** (169 mg, 1.04 mmol) was added to a stirred solution of imine **10b** (168 mg, 1.04 mmol) in chloroform (5 mL). After stirring overnight at room temperature, the solution was extracted with 10% aqueous sodium bicarbonate (3 × 10 mL). The basic extracts were acidified with concentrated HCl and then extracted with chloroform (3 × 5 mL). Evaporation of solvent from the chloroform extracts gave a white solid that was recrystallized from aqueous ethanol: 163 mg (48%); mp 188–191 °C; IR (KBr) 3100, 1725, 1610, 1400, 1140 cm^{-1}; NMR δ 8.25–7.00 (m, 9 H), 5.50 (d, 1 H, J = 6 Hz), 4.62 (d, 1 H, J = 6 Hz), 1.49 (s, 9 H); mass spectrum, m/e (relative intensity) 323 (M^+, 9), 262 (100), 129 (15), 91 (11), 84 (22), 73 (13), 71 (35), 69 (59), 67 (24), 65 (17). Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.56; H, 6.65; N, 4.34.

***cis*-*N*,3-Diphenyl-4-carboxy-3,4-dihydro-1(2*H*)-isoquinolone (*cis*-11c).** Imine **10c** (112 mg, 0.62 mmol) was added to a solution of anhydride **5** (100 mg, 0.62 mmol) in ethylene dichloride (10 mL) at reflux. The reaction mixture was heated at reflux for 15 min under a nitrogen atmosphere. The reaction mixture was stored at room temperature overnight before filtration of the solid: 85 mg (40%); mp 209–211 °C; IR (KBr) 3060, 3020, 1725, 1630, 1160, 680 cm^{-1}; NMR ($CDCl_3$ + Me_2SO-d_6) δ 8.25–6.85 (m, 14 H), 5.35 (d, 1 H, J = 6 Hz), 4.81 (d, 1 H, J = 6 Hz); mass spectrum, m/e (relative intensity) 343 (M^+, 11), 182 (67), 181 (100), 180 (61), 134 (59), 105 (36), 89 (10), 78 (20), 77 (84). Anal. Calcd for $C_{22}H_{19}NO_3$: C, 76.95; H, 4.99; N, 4.08. Found; C, 76.83; N, 5.06; N, 3.71.

***cis*-*N*-Isobutyl-3-phenyl-4-carboxy-3,4-dihydro-1(2*H*)-isoquinolone (*cis*-11d).** Anhydride **5** (0.50 g, 3.1 mmol) was added to a solution of imine **10d** (0.50 g, 3.1 mmol) in chloroform (10 mL). The reaction mixture was stirred for 30 min and then allowed to stand for 7 h at room temperature. The solvent was evaporated, and the residue was crystallized from aqueous methanol: 313 mg (31%); mp 178–181 °C; IR (KBr) 2940, 2910, 1735, 1620, 1595, 1570, 1470, 1445, 1270, 1200, 1160 cm^{-1}; NMR δ 8.30–7.99 (m, 9 H), 5.04 (d, 1 H, J = 6 Hz), 4.69, (d, 1 H, J = 6 Hz), 4.01 (dd, 1 H, J = 13 and 7 Hz), 2.60–1.75 (m, 2 H), 0.99 (d, 3 H, J = 6 Hz), 0.96 (d, 3 H, J = 6 Hz). Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.30; H, 6.65; N, 4.43.

***cis*-*N*-Isopropyl-3-phenyl-4-carboxy-3,4-dihydro-1(2*H*)-isoquinolone (*cis*-11f).** Anhydride **5** (1.1064 g, 6.82 mmol) was added a solution of imine **10f** (1.0039 g, 6.82 mmol) in chloroform (20 mL), and the mixture was stirred at room temperature overnight. The solvent was evaporated and the solid residue recrystallized from ethanol: 1.1474 g (54%); mp 186–188 °C; IR (KBr) 3400–2400, 1740, 1615, 1150 cm^{-1}; NMR δ 8.21–8.10 (m, 1 H), 7.63–6.99 (m, 8 H), 5.17 (d, 1 H, J = 6 Hz), 4.93 (m, 1 H), 4.57 (d, 1 H, J = 6 Hz), 1.34 (d, 3 H, J = 7 Hz), 0.88 (d, 3 H, J = 7 Hz). Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 5.90, N, 4.53. Found: C, 73.97, H, 6.28; N, 4.56.

***trans*-*N*-Methyl-5-(*p*-chlorophenyl)-4-(methoxycarbonyl)-4-phenyl-2-pyrrolidinone (*trans*-19a).** A mixture of anhydride **18** (151 mg, 0.86 mmol) and imine **8b** (130 mg, 0.85 mmol) in chloroform (5 mL) was heated at reflux for 1 h. The solvent was evaporated and the oily residue solidified on standing. The solid was dissolved in acetone (5 mL), and then K_2CO_3 (59 mg, 0.43 mmol) and dimethyl sulfate (81 μL) were added. The suspension was stirred overnight at room temperature and filtered. Evaporation of the solvent gave a white solid. Crystallization from aqueous methanol gave 249 mg of solid that was again recrystallized from aqueous methanol to give the pure trans ester: 109 mg (39%); mp 147–149 °C; IR (KBr) 3060, 2940, 1725, 1680, 1410, 1235, 1080, 1040 cm^{-1}; NMR δ 7.18–6.77 (m, 9 H), 5.48 (s, 1 H), 3.73 (s, 3 H), 3.25 (s, 1 H), 3.23 (s, 1 H), 2.76 (s, 3 H). Anal. Calcd for $C_{19}H_{18}NO_3Cl$: C, 66.38; N, 5.28; N, 4.07; Cl, 10.31. Found: C, 66.35; H, 5.43; N, 3.96; Cl, 10.46.

***cis*-*N*-Methyl-5-(*p*-chlorophenyl)-4-(methoxycarbonyl)-4-phenyl-2-pyrrolidinone (*cis*-19a).** The mother liquor from the first recrystallization above gave a second crop yielding the cis diastereomer: 10 mg (3.5%); mp 141–142 °C; IR (KBr) 3060, 2930, 1740, 1690 cm^{-1}; NMR δ 7.37–7.18 (m, 9 H), 5.04 (s, 1 H), 3.69 (d, 1 H, J = 17 Hz), 3.27 (s, 3 H), 2.78 (s, 3 H), 2.62 (d, 1 H, J = 17 Hz).

***trans*-*N*-Methyl-4-carboxy-4,5-diphenyl-2-pyrrolidinone (*trans*-19b).** Phenylsuccinic anhydride **18** (0.74 g, 4.2 mmol) was added to a solution of imine **8c** (0.50 g, 4.2 mmol) in chloroform (25 mL). The reaction mixture was stirred at room temperature overnight, and the solvent was then evaporated to give a white solid. The solid was recrystallized from methanol: 0.62 g (50%); mp 294–297 °C; IR (KBr) 3000, 2910, 2740, 2500, 1700, 1630, 1260, 1220 cm^{-1}; NMR δ 7.40–6.80 (m, 10 H), 5.54 (s, 1 H), 3.29 (s, 2 H), 2.75 (s, 3 H); mass spectrum, *m/e* (relative intensity) 295 (M^+, 3), 148 (18), 120 (100), 118 (29), 103 (23), 91 (11), 77 (24). Anal. Calcd for $C_{18}H_{27}NO_3$: C, 73.20, H, 5.80; N, 4.74. Found: C, 73.35; H, 5.78; N, 4.89.

***trans*-*N*-Methyl-4-carboxy-5-(*p*-methylphenyl)-4-phenyl-2-pyrrolidinone (*trans*-19c).** Anhydride **18** (1.32 g, 7.49 mmol) and imine **8d** (1.00 g, 7.51 mmol) were heated at reflux in chloroform (20 mL) for 2 h. After the mixture was allowed to stand for 2 days, the solid was filtered and then dissolved in hot chloroform (20 mL) containing methanol (3 mL). Two different crystalline forms precipitated and were separated manually to give the trans isomer [632 mg (27%)] as blocks and the cis isomer [474 mg (20%)] as a powder. On evaporation of the solvent, additional trans isomer (903 mg) was obtained. The total yield of trans isomer was 1.535 g (66%): mp 239–241 °C; IR (KBr) 3400–2200, 1710, 1640, 1260, 1220 cm^{-1}; NMR δ 7.07 (s, 5 H), 6.82 (m, 4 H), 5.48 (s, 1 H), 3.22 (s, 2 H), 2.69 (s, 3 H), 2.18 (s, 3 H). Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.14; N, 4.53. Found: C, 73.58; H, 6.25; N, 4.44.

***cis*-*N*-Methyl-4-carboxy-5-(*p*-methylphenyl)-4-phenyl-2-pyrrolidinone (*cis*-19c).** This substance was isolated as described above: mp 269–270 °C; IR (KBr) 3400–2400, 1730, 1650 cm^{-1}; NMR δ 7.36 (s, 5 H), 7.16 (s, 4 H), 5.05 (s, 1 H), 3.67 (d, 1 H, J = 17 Hz), 2.75 (s, 3 H), 2.54 (d, 1 H, J = 17 Hz), 2.34 (s, 3 H). Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.14; N, 4.53. Found: C, 73.82; H, 6.41; N, 4.30.

***trans*-*N*-Methyl-4-carboxy-5-(*p*-methoxyphenyl)-4-phenyl-2-pyrrolidinone (*trans*-19d).** Anhydride **18** (1.073 g, 6.09 mmol) and imine **8e** (0.909 g, 6.09 mmol) were heated at reflux in chloroform for 1 h. The solvent was evaporated and the solid residue recrystallized from methanol to yield the cis diastereomer, 188 mg (9%). The mother liquor was allowed to evaporate slowly at room temperature for several days, resulting in the formation of a second crop (174 mg) that consisted of a diastereomeric mixture of pyrrolidinones. The third crop consisted of pure trans isomer: 530 mg (27%); mp 185–186 °C; IR (KBr) 3400–2400, 1710, 1650, 1240, 1220 cm^{-1}; NMR δ 7.07 (s, 5 H), 6.76 (d, 2 H, J = 9 Hz), 6.61 (d, 2 H, J = 9 Hz), 5.49 (s, 1 H), 3.68 (s, 3 H), 3.25 (s, 2 H), 2.72 (s, 3 H). Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.30. Found: C, 69.93; H, 5.59; N, 4.46.

***cis*-*N*-Methyl-4-carboxy-5-(*p*-methoxyphenyl)-4-phenyl-2-pyrrolidinone (*cis*-19d).** The cis isomer was prepared and isolated as described above: mp 263–264 °C; IR (KBr) 3400–2200, 1720, 1650, 1240 cm^{-1}; NMR δ 7.35 (s, 5 H), 7.17 (d, 2 H, J = 9 Hz), 6.89 (d, 2 H, J = 9 Hz), 5.06 (s, 1 H), 3.80 (s, 3 H), 3.65 (d, 1 H, J = 17 Hz), 2.75 (s, 3 H), 2.50 (d, 1 H, J = 17 Hz). Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.30. Found: C, 69.90; H, 6.08; N, 4.32.

***cis*-*N*-Methyl-4-carboxy-5-[*p*-(dimethylamino)phenyl]-4-phenyl-2-pyrrolidinone (*cis*-19e).** Anhydride **18** (160 mg, 0.91 mmol) and imine **8f** (147 mg, 0.91 mmol) were heated at reflux in chloroform (5 mL) for 40 min. The solution was allowed to stand for 2 days, and the crystalline solid was filtered: 39 mg (12.7%); mp 260–261 °C; IR (KBr) 3400–2400, 1710, 1650, 1240, 1220, 680 cm^{-1}; NMR δ 7.31 (s, 5 H), 7.01 (d, 2 H, J = 9 Hz), 6.64 (d, 2 H, J = 9 Hz), 5.00 (s, 1 H), 3.50 (d, 1 H, J = 17 Hz), 2.88 (s, 6 H), 2.62 (s, 3 H), 2.30 (d, 1 H, J = 17 Hz).

***trans*-*N*-Ethyl-4-(methoxycarbonyl)-4,5-diphenyl-2-pyrrolidinone (*trans*-20a).** A mixture of anhydride **18** (0.89 g, 5 mmol) and imine (0.67 g, 5 mmol) was heated at reflux in chloroform (20 mL) for 5 h. The solvent was evaporated and the residue dissolved in acetone (30 mL). Anhydrous K_2CO_3 (0.35 g) and dimethyl sulfate (0.64 g) were added, and the reaction mixture was stirred at room temperature overnight, filtered, and evaporated. Crystallization from aqueous methanol gave two crops of pure trans ester: 0.56 g (36%); mp 146–148 °C; IR (KBr) 3040, 2960, 1720, 1680, 1420, 1220 cm^{-1}; NMR δ 7.12–6.90 (m, 10 H), 5.63 (s, 3 H), 3.77 (m, 1 H), 3.72 (m, 3 H), 3.35 (d, 1 H, J = 16 Hz), 3.28 (d, 1 H, J = 16 Hz), 2.73 (m, 1 H), 1.07 (t, 3 H, J = 6 Hz). Anal. Calcd for $C_{20}H_{22}NO_3$: C, 74.28; N, 6.55; N, 4.33. Found: C, 74.47; H, 6.74; N, 4.05.

***trans*-*N*-Isopropyl-4-(methoxycarbonyl)-4,5-diphenyl-2-pyrrolidinone (*trans*-20b).** Anhydride **18** (0.89 g, 5.05 mmol) and imine **10f** (0.74 g, 5.03 mmol) were heated at reflux in chloroform (30 mL) for 1 h. The solvent was evaporated, and the residue was dissolved in acetone (30 mL). Anhydrous K_2CO_3 (0.35 g) and dimethyl sulfate (0.64 g) were added, and the mixture was stirred overnight at room temperature. The reaction mixture was filtered, and the solvent was evaporated to yield a white solid, which was then recrystallized from methanol. The first two crops consisted of the trans ester **20b**: 609 mg (36%); mp 170–171 °C; IR (KBr) 3040, 2960, 1720, 1680, 1420, 1220, 1235 cm^{-1}; NMR δ 7.05 (m, 10 H), 5.64 (s, 1 H), 4.30 (m, 1 H, J = 7 Hz), 3.79 (s, 3 H), 3.40 (d, 1 H, J = 17 Hz), 3.24 (d, 1 H, J = 17 Hz), 1.25 (d, 3 H, J = 7 Hz), 0.82 (d, 3 H, J = 7 Hz); high-resolution mass spectrum, calcd 337.1678, found 337.1680. Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.52; H, 7.17; N, 4.23.

***cis*-*N*-Isopropyl-4-(methoxycarbonyl)-4,5-diphenyl-2-pyrrolidinone (*trans*-20b).** The third crop from the mother liquor above consisted of the cis diastereomer: 50 mg (3%); mp 142–144 °C; IR (KBr) 3040, 2960, 1725, 1665, 1420, 1230 cm^{-1}; NMR δ 7.50–7.20 (m, 10 H), 5.18 (s, 1 H), 4.25 (m, 1 H), 3.80 (d, 1 H, J = 17 Hz), 3.17 (s, 3 H), 2.70 (d, 1 H, J = 17 Hz), 1.15 (d, 3 H, J = 7 Hz), 0.82 (d, 3 H, J = 7 Hz). Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.83; H, 6.99; N, 4.23.

***trans*-*N*-*tert*-Butyl-4-carboxy-4,5-diphenyl-2-pyrrolidinone (*trans*-20c).** A solution of anhydride **18** (574 mg, 3.26 mmol) and imine **10b** (521 mg, 3.23 mmol) in chloroform (20 mL) was heated at reflux for 1 h. The solvent was evaporated, and the solid residue was recrystallized from aqueous ethanol: 196 mg (18%); mp 213–215 °C; IR (KBr) 3600–2200, 2960, 1710, 1630, 1410, 1230, 1190 cm^{-1}; NMR δ 7.07–7.02 (m, 10 H), 5.78 (s, 1 H), 3.35 (d, 1 H, J = 17 Hz), 3.03 (d, 1 H, J = 17 Hz), 1.35 (s, 9 H).

***cis*-*N*-*tert*-Butyl-4-carboxy-4,5-diphenyl-2-pyrrolidinone (*cis*-20c).** A mixture of anhydride **18** (285 mg, 1.62 mmol) and imine **10b** (258 mg, 1.60 mmol) in chloroform (10 mL) was stirred for 2 days at room temperature. The solvent was evaporated, and the solid residue was recrystallized from aqueous ethanol: 126 mg (23%); mp 215–216 °C; IR (KBr) 3600–2200, 2975, 1700, 1630, 1400, 1260, 1230, 1190 cm^{-1}; NMR δ 7.52–7.31 (m, 10 H), 5.39 (s, 1 H), 3.70 (d, 1 H, J = 17 Hz), 2.50 (d, 1 H, J = 17 Hz), 1.30 (s, 9 H); high-resolution mass spectrum, calcd 337.1678, found 337.1681.

General Procedure for the Determination of the Ratios of Diastereomeric Isoquinolones Reported in Table I. Equivalent amounts of imine and anhydride **5** (usually ca. 0.5 mmol of each) were added to the solvent, and the reaction mixture was stirred at room temperature overnight. The solvent was then evaporated, and the ratios of the diastereomers were determined by NMR integration. When formamide was employed as the solvent, the reaction mixture was diluted with a saturated aqueous NaCl solution (10 mL) and the resulting suspension was extracted with chloroform (2 × 10 mL). The solvent was then evaporated from the extracts and the residue utilized for determination of the ratios of diastereomers by NMR integration.

General Procedure for the Determination of the Ratios of Diastereomeric Pyrrolidinones Reported in Table IV. Anhydride **18** and imine (5 mmol of each) were heated at reflux in chloroform (30 mL) for 1 h. The solvent was then evaporated, and acetone (30 mL) was added to the residue. Anhydrous K_2CO_3 (0.35 g) and dimethyl sulfate (5 mmol) were then added, the reaction mixture was stirred overnight and filtered, and solvent was evaporated from the filtrate. The ratios of diastereomeric methyl esters were then determined by NMR integration.

General Procedure for Competition Experiments of Imine 8c with Imines 10a–c for Reaction with Homophthalic Anhydride (5). Imine **8c** (3.5 mmol) and one of the imines **10a–c** (3.5 mmol) were dissolved in chloroform (20 mL). Homophthalic anhydride (70 mg, 0.43 mmol) was added, and the reaction mixture was stirred 2 h and then extracted with 10% aqueous $NaHCO_3$. The combined extracts were acidified with concentrated HCl and

extracted with chloroform (3 × 5 mL). The combined organic extracts were evaporated to yield a light yellow solid. The NMR spectra of the products indicated that they were exclusively **9c** in yields ranging from 72 to 138 mg.

Competition Experiment of Benzaldehyde (16) and Benzylidenemethylamine (8c) for Reaction with Homophthalic Anhydride (5). Homophthalic anhydride (5; 0.76 g, 4.7 mmol) was added at room temperature to a mixture of benzaldehyde (16; 0.50 g, 4.7 mmol) and *N*-benzylidenemethylamine (8c; 0.56 g, 4.7 mmol) in chloroform (15 mL) containing triethylamine (1 mL). An immediate exothermic reaction occurred upon addition of the anhydride. The reaction mixture was stirred at room temperature for 1 h. The product obtained after evaporation of the solvent was subjected to NMR analysis, which indicated that the ratio of the imine-derived product 7 to the aldehyde-derived product 17 was 3:1.

The Reaction of Metal Fluorides with *unsym*-Azetidinone Disulfides and 2β-(Halomethyl)penams. The 3β-Fluoro-3α-methylcephams

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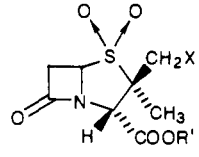
Fluorination studies on *unsym*-azetidinone disulfides and 2β-[halo(Cl- and Br-)methyl]penams with metal fluorides are described. The *unsym*-azetidinone disulfides with AgF, in CH_2Cl_2, produce the 3β-fluoro-3α-methylcephams in low yields. The reaction of the 2β-[halo(Cl- and Br-)methyl]penams with AgF or HgF_2 gave the 3β-fluoro-3α-methylcepham as the only identifiable fluorine-containing compound; the reaction was dependent on the solvent, time, temerature, and the 2β-[halo(Cl- or Br-)methyl]penam used. The ^{19}F, ^{13}C, and ^1H NMR spectral data of the 3β-fluoro-3α-methylcepham and its sulfoxide and sulfone are reported.

During the course of our previous studies on the very potent YTR class of β-lactamase inhibitors **1a**,[1-4] we had occasion to synthesize and study the 6,6-dihydro-2β-(chloro-, 6,6-dihydro-2β-(bromo-, and 6,6-dihydro-2β-(azidomethyl)penam 1,1-dioxides **1b** (X = Cl, Br, N_3).[2] Gottstein and co-workers and we independently found that these compouds also possessed good β-lactamase inhibitory activity.[5-8] In continuation of this work we have been investigating methods for the synthesis of 2β-(fluoromethyl)penam 1,1-dioxides **1c** (X = F), since the fluoromethyl substituent in organic molecules can function as an irreversible enzyme inhibitor.[9]



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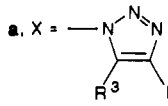
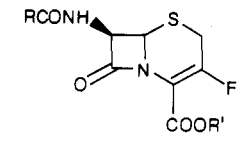
a, X =  **b**, X = Cl, Br, N_3 **c**, X = F

Reagents such as diethylaminosulfur trifluoride (DAST),[10] 2-chloro-1,1,2-trifluorotriethylamine (CTT),[11] or piperidinosulfur trifluoride (PST)[12] have been extensively used for the conversion of hydroxyl to fluoro groups. Utilizing such reagents, 3-fluorocephems **2**, 3-(fluoromethyl)cephems **3**, and 3-(difluoromethyl)cephems **4** have been made by Muller and co-workers,[13] and 6-(fluoroisopropyl)carbapenem **5** has been made by Mak and Wagner.[14] We found that the reaction of 2β-(hydroxymethyl)penams[15] with DAST under reflux in methylene chloride gave mainly the starting compound with small amounts of a new product identified as 3β-fluoro-3α-methylcephams **7** (X = F, *n* = 0).



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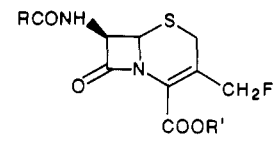

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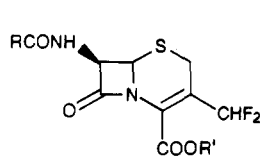

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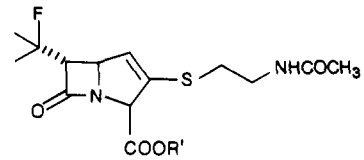

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A very recent abstract by von Daehne and co-workers reports the formation of a mixture of 6β-bromo-2β-(fluoromethyl)penam **6** (R = Br, X = F), 7β-bromo-3β-fluorocepham **7** (R = Br, X = F, *n* = 0), and 7β-bromocephem **8** (R = Br, *n* = 0), by the nucleophilic substitution of

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