Concerning the mechanism of the Friedländer quinoline synthesis

Joseph M. Muchowski and Michael L. Maddox

Abstract: Detailed experiments regarding the mechanism of the Friedländer synthesis of quinolines from *o*-aminobenzaldehydes and simple aldehydes or ketones are described. Under the basic or acidic conditions commonly used in this reaction, it is concluded that the first step involves a slow intermolecular aldol condensation of the aldehyde or ketone with the *o*-aminobenzaldehyde. The aldol adduct **5** generated in this manner then undergoes very rapid cyclization to **4**, which subsequently loses water to produce the quinoline derivative **8**. Both **5** and **4** are too short lived to be detectable (TLC), even when deliberately generated by other means. It is also shown that *E*-enones corresponding to **6**, i.e., the aldol dehydration product, are converted into quinolines (e.g., **21a** and **21b** from **17a** and **17b**) under basic or acidic conditions. Such enones are not detected as intermediates in the base-induced Friedländer synthesis, even though certain congeners (**17b**) would be easily observable. Under acidic conditions these enones are too short lived to be detectable. Schiff bases derived from 2-aminobenzaldehyde (**18a**) and aldehydes or ketones can be generated under special conditions, but they show reactivity patterns different from those seen in the usual Friedländer condensations. Thus, the ytterbium-triflate-catalyzed reaction of aldehydes with **18a** at room temperature in toluene generates the *E*-Schiff bases (**33**, R^1 = H), from which isomeric mixtures of tetrahydroquinoline derivatives **26** are formed exclusively. At higher temperatures, the *E*-Schiff bases **33** are isomerized to the *Z*-Schiff bases **34**, from which the 3-substituted quinoline derivatives **24** are formed as the major products under appropriate conditions. Also, the ytterbium-triflate-catalyzed reaction of **18a** with the pyrrolidine enamines of the methyl-*n*-alkylketones **38a**,**b** produces mixtures in which the 2-monosubstituted kinetic products **37b**,**d** predominate over the 2,3-disubstituted thermodynamic products **21c**,**e** by a factor of 4:1 to 5:1. These results are opposite to those observed under the usual basic or acidic Friedländer reactions with methyl-*n*-alkylketones, where the thermodynamic products are usually strongly favored. The unusual kinetic:thermodynamic product ratios observed with **38a**,**b** are ascribed to the generation and rapid cyclization of mixtures of the Schiff bases **35** and **36**, in which the kinetic isomer **35** is highly predominant.

Key words: mechanism, Friedländer synthesis, quinolines, intramolecular aldol reactions, Schiff bases, tetrahydroquinolines, high kinetic:thermodynamic product ratios.

Résumé : On rapporte les détails d'expériences réalisées dans le but d'élucider le mécanisme de la synthèse des quinoléines de Friedländer à partir d'*o*-aminobenzaldéhydes et d'aldéhydes ou des cétones simples. On en déduit que, dans les conditions légèrement acides ou basiques utilisées pour cette réaction, la première étape implique une condensation aldolique intermoléculaire lente de l'aldéhyde ou de la cétone avec l'*o*-aminobenzaldéhyde. L'adduit aldolique ainsi généré, **5**, subit alors une cyclisation très rapide en **4** qui perd subséquemment de l'eau pour conduire au dérivé **8** de la quinoléine. Les temps de vie des intermédiaires **5** et **4** sont tous les deux beaucoup trop courts pour qu'on puisse les détecter (CCM), même lorsqu'on tente de les générer par d'autres méthodes. On a aussi montré que les *E*-énones correspondant à **6**, c'est-à-dire le produit de déshydratation de l'aldol, peuvent être transformées en quinoléines (par exemple, **21a** et **21b** à partir de **17a** et **17b**) dans des conditions acides ou basiques. Ce type d'énone n'est pas détecté comme intermédiaire dans la synthèse de Friedländer induite par les bases même si certains congénères (**17b**) seraient facilement observables. Dans des conditions acides, les temps de vie de ces énones sont trop courts pour qu'on puisse les détecter. Les bases de Schiff du 2-aminobenzaldéhyde (**18a**) avec les aldéhydes ou les cétones peuvent être générées dans des conditions spéciales, mais leurs patrons de réactivité sont différents de ceux observés dans les condensations de Friedländer habituelles. Ainsi, la réaction catalysée par le triflate d'ytterbium des aldéhydes avec **18a**, à la température ambiante et dans le toluène, conduit à la formation de bases de Schiff de stéréochimie *E*- (**33**, R^1 = H) à partir desquelles il se forme uniquement des mélanges isomères de dérivés tétrahydroquinoléines **26**. À des températures plus élevées, les bases de Schiff de stéréochimie *E*- (**33**) s'isomérisent en bases de stéréochimie *Z*- (**34**) à partir desquelles, dans des conditions appropriées, les produits qui se forment d'une façon prépondérante sont des dérivés de la quinoléine substitués en position 3 (**24**). De plus, la réaction catalysée par le triflate d'ytterbium du produit **18a** avec

Received 3 June 2003. Published on the NRC Research Press Web site at http://canjchem.nrc.ca on 27 February 2004.

Dedicated to Professor Victor Snieckus in recognition of his numerous fundamental contributions to heteroatom directed metalations.

J.M. Muchowski[1] and M.L. Maddox. Chemistry, Roche Palo Alto, 3431 Hillview Avenue, Palo Alto, CA 94304, U.S.A.

[1]Corresponding author (e-mail: joseph.muchowski@roche.com).

 doi: 10.1139/V03-211

des énamines formées par réaction de la pyrrolidine sur les méthylalkylcétones **38a,b** conduit à la formation de mélanges dans lesquels les produits cinétiques portant un substituant en position 2 (**37b,d**) prédominent par rapport aux produits thermodynamiques disubstitués en 2,3 (**21c,e**) par un facteur allant de 4:1 à 5:1. Ces résultats sont opposés à ceux observés dans les conditions usuelles des réactions de Friedländer acide ou basique des méthylalkylcétones dans lesquelles les produits thermodynamiques sont généralement fortement favorisés. Les rapports inhabituels de produits cinétiques et thermodynamiques observés avec les produits **38a,b** sont attribués à la génération et à la cyclisation rapide de mélanges des bases de Schiff **35** et **36** dans lesquels l'isomère cinétique **35** est fortement prédominant.

Mots clés : mécanisme, synthèse de Friedländer, quinoléines, réactions aldoliques intramoléculaires, bases de Schiff, tétrahydroquinoléines, rapport élevé des rapports de produits cinétiques et thermodynamiques.

[Traduit par la Rédaction]

Introduction

The formation of a quinoline derivative by the condensation of an aromatic *o*-aminoaldehyde or *o*-aminoketone with an aldehyde or a ketone containing a methylene group alpha to the carbonyl moiety, under basic or acidic conditions, is known as the Friedländer synthesis (1–5). The development of the heteroatom-directed *o*-metalation of aromatic systems (6), which has provided facile access to a variety of *o*-aminoaldehydes and *o*-aminoketones, has made the Friedländer reaction one of the most reliable of all quinoline syntheses. Basic reaction conditions are particularly efficient for the generation of quinoline derivatives from ketones and *o*-aminoaldehydes, whereas the condensation of ketones with *o*-aminoketones is best effected in acidic media. The most notable advantage of the Friedländer synthesis is that the positions of the substituents in the homocyclic ring are fixed by the structure of the *o*-aminocarbonyl component, and the regiochemistry of the substituents in the heterocyclic ring is predictable because nonsymmetrical ketones usually give rise to the quinoline derived from the thermodynamic enolate as the major or exclusive product.

Although the general features of the Friedländer synthesis are well understood, there is still a considerable degree of uncertainty regarding the mechanistic details of the process. Two distinctly different reaction pathways have been suggested (4, 5) to account for the facts. One involves the rate-determining formation of the Schiff base **3** (Scheme 1), followed by an intramolecular aldol-type condensation to the hydroxyimine **4** and subsequent loss of water therefrom to produce the quinoline **8**. In the other proposal, the rate-limiting step is the generation of the intermolecular aldol intermediate **5**, which proceeds to the quinoline via the above mentioned hydroxyimine **4**.

Evidence in support of each mechanistic proposal exists, but that for the intermolecular aldol process is very rare. Thus, a unique example of the isolation of the purported aldol adduct **9** (Scheme 2) in the piperidine-catalyzed, room temperature reaction of 2-aminonicotinaldehyde with 1,4-cyclohexanedione has been described (7). Although an NMR spectrum of **9** could not be obtained, analytical (CHN) and IR data and the nearly quantitative generation of the expected quinoline derivative on mere heating in toluene solution were consistent with the β-ketol structure. On the other hand, Schiff bases **10** bearing a stabilizing substituent in the β-position have been generated in several instances (8–10), although not under the usual Friedländer conditions (see below). These entities, which must exist in the vinylogously stabilized forms **11**, have been cyclized under both basic (8, 10) and acidic (9) conditions. No Schiff base derived from a simple aldehyde or ketone and an aromatic *o*-aminocarbonyl compound has ever been isolated.

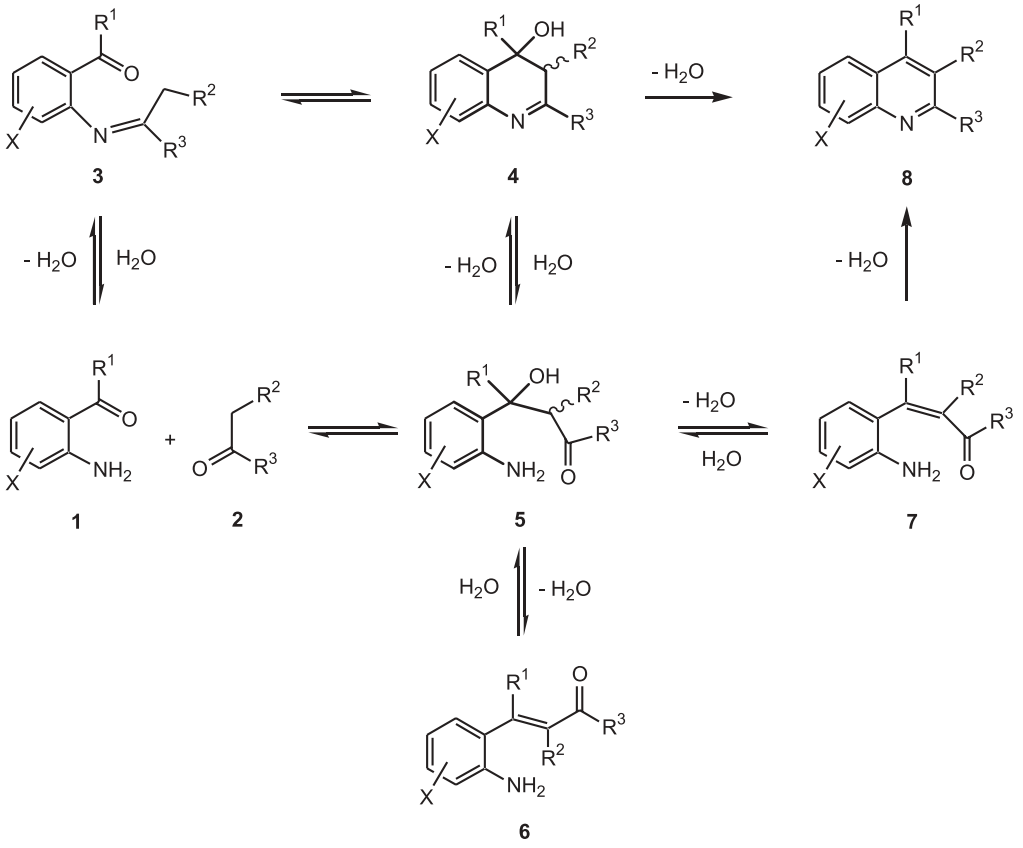
Given the weight of the evidence cited above, the Friedländer synthesis is usually considered to occur via an intermediate Schiff base. The intermolecular aldol mechanism has also been considered improbable because of the expected facile formation of the conjugated unsaturated carbonyl compound **6** of *E*-geometry and the unlikely conversion of this species into the quinoline (via the *Z*-stereoisomer **7**) (5). Nevertheless, recently devised versions of the Friedländer synthesis show that neither **5** nor **6** can a priori be discounted as intermediates (11–14). Indeed, in a generally overlooked 1883 publication, Drewsen (15) reported that the nitroenone **12** was converted into 2-methylquinoline with stannous chloride in hydrochloric acid medium, although neither the exact conditions nor the yield were reported!

The putative generation of aldol intermediates corresponding to **5** (11, 12) and the isolation of enones (14) and the enals related to **6** (R^1, R^3 = H) (11) as *N*-acylated congeners, as well as the conversion of these species and **12** into quinolines, encouraged us to take another look at the mechanism(s) of the Friedländer synthesis. Herein are described our attempts to generate each of the intermediates shown in Scheme 1 and to establish the presence or absence thereof under conditions typically used in this synthesis.

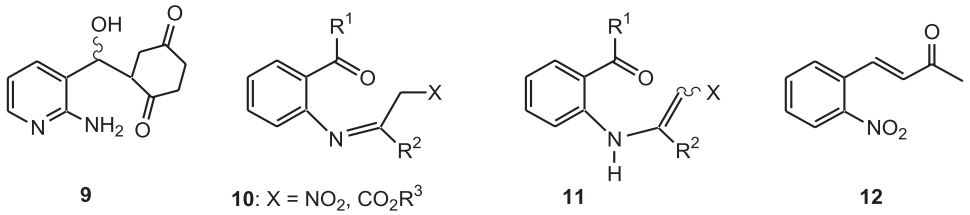
Results and discussions

The starting materials required for this study were prepared as shown in Scheme 3. Thus, the sodium-hydroxide-promoted condensation of the aldehydes **13** with acetone or 2-butanone under conditions similar to or slightly modified from those of Baeyer and Drewsen (16) gave the β-ketols **14** as the major products. These were accompanied by minor amounts of the kinetic product **15**, from 2-butanone and **13a**, and the enone **16c**, from **13b** and acetone. The nitroenones **16a** and **16b**, obtained from the β-ketols **14a** and **14b** by dehydration with hot acetic anhydride, were converted into the amines **17a** and **17b** by reduction with iron powder and ammonium chloride in a two-phase system at room temperature (17, 18). The very unstable enal **17c** was prepared by this technique as well. This mild, chemospecific reducing system is also the preferred one for preparing 2-aminobenzaldehydes

Scheme 1. Possible mechanisms of the Friedländer quinoline synthesis.



Scheme 2.

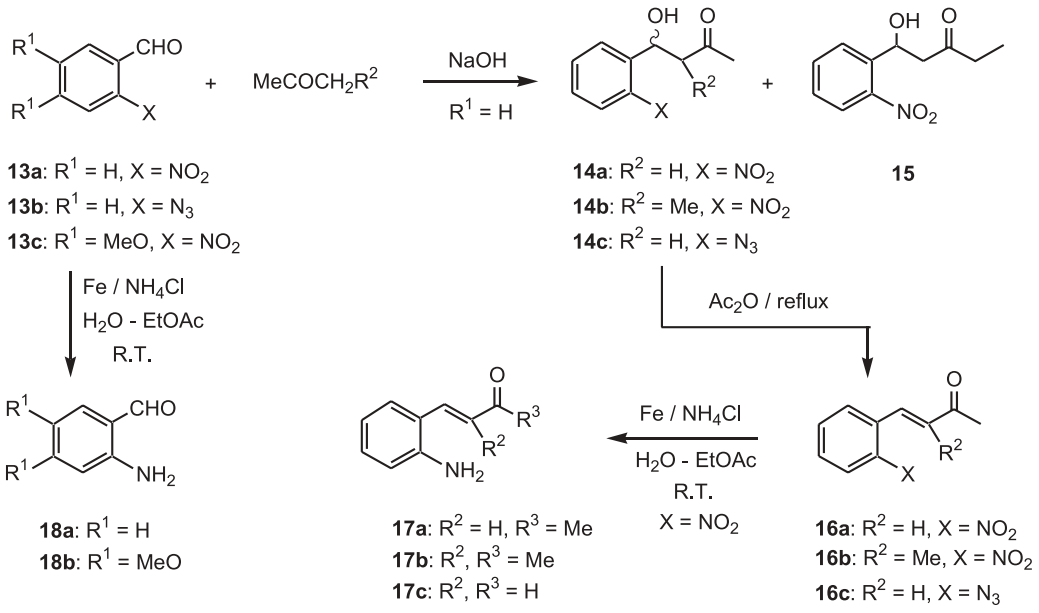


(**18**) from 2-nitrobenzaldehydes (**13a** and **13c**). Indeed, for the synthesis of 2-aminobenzaldehyde itself, it is far superior in terms of yield (86%–93%) and ease of workup than is the commonly used method (19) or its recent modification (20).

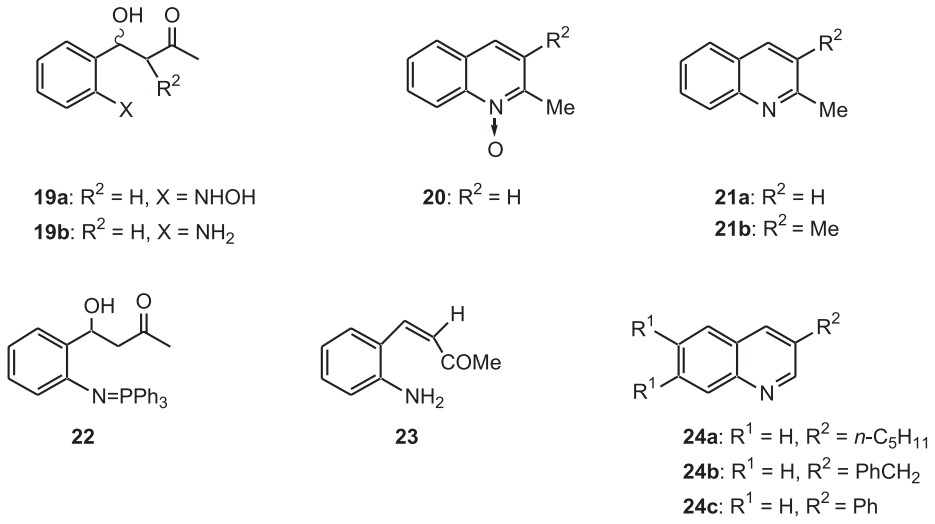
The generation of an aldol intermediate analogous to **5** (Scheme 1) was examined first. Reduction of the β-ketol **14a** with the iron – ammonium chloride system gave 2-methylquinoline-*N*-oxide (**20**, Scheme 4, Table 1) in 76% yield and a trace of 2-methylquinoline (**21a**). The *N*-oxide **20** is obviously produced by the cyclization of the very nucleophilic intermediate hydroxylamine **19a**. The nearly exclusive generation of **20** under these conditions is expected, since during the reduction of the nitro compounds **13a**, **16a**, and **16b** at least, the rapid formation of the intermediate hydroxylamines and the much slower appearance of the amines is easily seen by thin layer chromatography (TLC). In contrast, catalytic reduction of **14a** over Pd–C catalyst at atmospheric pressure gave a 4:1 mixture favoring the *N*-oxide. Somewhat similar results have been reported for the catalytic reduction of certain Baylis–Hillman (21) products derived from 2-nitrobenzaldehyde (13). Reduction of the azido compound **14c**, where the amine **19b** must be an intermediate, using the iron – ammonium chloride method gave **21a** exclusively in high yield. No intermediates were detectable by TLC in these reductions; therefore, the lifetime of both the aldol intermediate **19b** and the cyclization product **4** (Scheme 1) enroute to the quinoline must be quite short. This assumption was verified for the latter intermediate by reaction of the azido compound **14c** with triphenylphosphine. No intermediate, not even the iminophosphorane **22**, was detectable by TLC during the course of the reaction, even at room temperature.

The *E*-enones **17a,b** were next studied as potential intermediates in the Friedländer synthesis. Under thermodynamic conditions, the base-catalyzed aldol condensation is reversible in all steps (22). For this reason, as well as because of

Scheme 3. Synthesis of the starting materials.



Scheme 4.



microscopic reversibility (23), it should be possible to convert the *E*-enones into the corresponding quinolines, possibly via the *Z*-enones **7** (see also ref. 24) under basic conditions. Indeed, when dissolved in aqueous ethanol containing 20 mol% sodium hydroxide, **17a** was cleanly converted into 2-methylquinoline (**21a**) after ca. 1 day at room temperature (Table 1). The reaction of 2-aminobenzaldehyde with excess acetone under very similar conditions produced **21a** more slowly but just as efficiently. These are the conditions described by Friedländer himself (2)! Even the aldehyde **17c** is very slowly transformed into quinoline with less than an equivalent of base at ambient temperature (entry 7). In contrast, the enone **17b** is stable under these conditions, but it is converted efficiently into 2,3-dimethylquinoline (**21b**) at reflux temperature using 3.3 equiv. of base. Excess sodium hydroxide is also required for the generation of **21b** from 2-aminobenzaldehyde and 2-butanone, but the reaction proceeds at room temperature (entry 9). It is noteworthy that the enone **17b** was not detectable during the course of the latter reaction, even though it would easily have been observable by TLC (intense yellow color on silica gel plates) had it been formed. Thus, although such enones clearly are viable intermediates, it is unlikely that they play a significant role in the alkali-induced version of the Friedländer quinolone synthesis. Hsaio et al. (14) have recently shown that the Horner–Emmons reaction of 2-aminonicotinaldehyde and β-ketophosphonates generated the expected naphthyridines via the *E*-enones, but they did not examine the corresponding Friedländer synthesis for these intermediates.

The question of a Schiff base intermediate **3** in the alkali-hydroxide-mediated version of the Friedländer synthesis can now be addressed with confidence. Under neutral conditions, 2-aminobenzaldehyde (**18a**) is remarkably resistant to reaction with ketones or aldehydes. For example, it can be recov-

Table 1. Formation of quinoline derivatives from putative Friedländer intermediates.

Entry	Starting materials	Conditions	Time (h)	Products (%)[a]
1	**14a**	Fe-NH_4Cl	1	**20** (76), **21a** (trace)[b]
2	**14a**	H_2, Pd–C	0.25	**20** (80)[c], **21a** (20)[c]
3	**14c**	Fe-NH_4Cl	12	**21a** (85)
4	**14c**	Ph_3P, Tol, Δ	2	**21a** (73)
5	**17a**	0.2 NaOH, EtOH-H_2O(3:1), RT	27	**21a** (83)
6	**18a** + Me_2CO	0.2 NaOH, EtOH-H_2O(4:3), RT	47	**21a** (80)
7	**17c**	0.8 NaOH, EtOH-H_2O(3:1), RT	75	Quinoline (63)
8	**17b**	3.3 NaOH, EtOH-H_2O(1:1), Δ	16	**21b** (83)
9	**18a** + MEK	3.3 NaOH, EtOH-H_2O(3:2), RT	7	**21b** (77)
10	**17c**	TFA, THF, RT	[d]	Tar
11	**17a**	1.5 mol L^{-1} HCl, Diox-H_2O(1:1), Δ	1	**21a** (82)
12	**17b**	1.5 mol L^{-1} HCl, Diox-H_2O(1:1), Δ	1	**21b** (87)
13	**18a** + Me_2CO	1.5 mol L^{-1} HCl, Diox-H_2O(1:1), Δ	2	**21a** (0)
14	**18a** + Me_2CO	cat. H_2SO_4-HOAc, Δ	18	**21a** (26)
15	**17a**	cat. H_2SO_4-HOAc, Δ	2	**21a** (35)
16	**17a**	hν, EtOH	16	**21a** (75)

Note: Tol = toluene; RT = room temperature; Diox = dioxan; cat. = catalytic H_2SO_4 in acetic acid..
[a]Yield of picrate except where indicated.
[b]TLC.
[c]Product ratio measured by NMR.
[d]Formation took place within seconds rather than hours.

ered unaltered after many hours at reflux temperature in acetone solution. Likewise, toluene solutions of **18a**, containing various aldehydes in excess, are stable at room temperature for long periods of time. Given the diminished reactivity of **18a** and its congeners toward aldehydes and ketones and the aqueous- and (or) alcohol-based media in which the alkaline hydroxide-mediated condensations are usually effected, a Schiff base intermediate in this version of the Friedländer synthesis is quite improbable.

The formation of quinoline derivatives from *N*-acylated congeners of **17c** in acidic media (11) and the relatively facile acid-induced isomerization of *Z*-enones to *E*-enones (24–28) augured well for the acid-promoted generation of quinolines from **17a-c**. The free enal **17c** was, however, rapidly destroyed, even under the mildly acidic conditions previously used (11) to cyclize the *N*-BOC congeners of **17c** (entry 10). By contrast, enones **17a**,**b** were converted into the quinolines **21a,b** in over 80% yields with 1.5 mol L^{-1} hydrochloric acid in 50% aqueous dioxane after only 1 h at reflux temperature. An attempt to prepare **21a** from 2-aminobenzaldehyde and acetone under these conditions resulted in the destruction of the starting materials. Quinoline **21a** was nevertheless slowly formed from these reactants, although only in 26% yield, when the reaction was carried out in acetic acid solution containing a catalytic amount of sulfuric acid (29) at reflux temperature. 2-Methylquinoline (**21a**) was also produced (35% yield) from the enone **17a** upon heating in the same reaction medium for 2 h. Although such enones could well be intermediates under those often-used acidic conditions, their short half-lives ensure that they would not be readily detectable, at least by TLC.

It was tacitly assumed that *Z*-enones were involved as tenuous intermediates in the conversion of the *E*-enones **17a,b** into the quinolines **21a,b**. Corroborative evidence that the *Z*-enones must indeed be very short lived was obtained by photolysis of **17a** in ethanolic solution. 2-Methylquinoline was produced as the sole product, but the presumed intermediate *Z*-enone **23** was undetectable by TLC.

Up to this point no convincing evidence for an intermediate Schiff base had been found under conditions commonly used in the Friedländer synthesis. It seemed reasonable, therefore, to attempt to generate such species from aldehydes and 2-aminobenzaldehyde (**18a**) under more classical conditions. Heating solutions of **18a** and 1.2 equiv. of *n*-heptanal, 3-phenylpropionaldehyde, or phenylacetaldehye, freshly generated from the corresponding bisulfite adducts, in toluene containing a catalytic amount (5 mol%) of *p*-toluenesulfonic acid monohydrate with separation of water, gave modest yields of 3-substituted quinolines **24a-c** (Table 2). These quinolines were formed extremely slowly, or not at all, at room temperature. The quinolines were also obtained under similar conditions and in comparable yields using ytterbium triflate (10 mol%) as the catalyst, except that the reaction periods were greatly reduced, and water separation was not necessary (Table 2, entries 2, 4, 6). In every case, independent of the catalyst used, TLC examination showed that several much less polar, yellow-colored, neutral substances were also formed, none of which was a Schiff base. *n*-Heptanal gave rise to one such material in relatively good yield (25%–43%, ytterbium triflate catalyst) as an oil with a mass spectral molecular weight of 416. This corresponds to the condensation of two molecules of heptanal and two molecules of **18a** with the loss of three molecules of water ($C_{28}H_{30}N_2O$). The IR spectrum showed absorptions at 3334, 2733, and 1659 cm^{-1}, consistent with the presence of aldehyde and NH groups strongly bonded to each other, and this was supported by the ^1H NMR spectrum (DMSO-d_6), with peaks at δ 9.80 and 8.91, respectively. In addition to

Table 2. Generation of quinolines from Schiff bases derived from RCH_2CHO (A) or $MeCOCH_2R$ (B) and **18a** or **18b**.

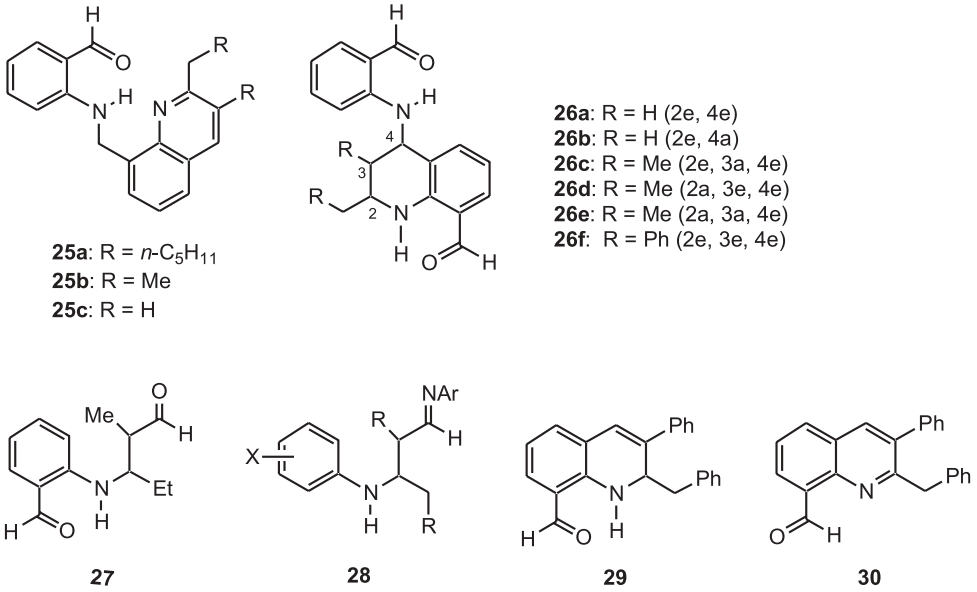
Entry	Starting material (R)	Catalyst	Time (h)	Products (%)[a]
1	**18a**; A(n-C_5H_{11})	TsOH	20	**24a** (34–36)[b]
2	**18a**; A(n-C_5H_{11})	$Yb(OTf)_3$	3 to 4	**24a** (29–47)[b]
3	**18a**; A($PhCH_2$)	TsOH	22	**24b** (28)[b]
4	**18a**; A($PhCH_2$)	$Yb(OTf)_3$	4	**24b** (28)[b]
5	**18a**; A(Ph)	TsOH	22	**24c** (31)[b]
6	**18a**; A(Ph)	$Yb(OTf)_3$	4	**24c** (44–53)[b]
7	**18a**; A(n-C_5H_{11})	$Yb(OTf)_3$	8(4)[c]	**24a** (47)[b]
8	**18b**; A(Ph)	$Yb(OTf)_3$	5(3)[c]	**24c** (80)
9	**18b**; A(n-C_5H_{11})	$Yb(OTf)_3$	6(3.75)[c]	**24d** (42)
10	**18b**; A(Ph)	$Yb(OTf)_3$	5(3)[c]	**24e** (78)
11	**18a**; B(Me)	$Yb(OTf)_3$	58(7)[d]	**21b** (48), **37a** (28)
12	**18a**; B(Et)	$Yb(OTf)_3$	48(7)[d]	**21c** (34.5), **37b** (41)
13	**18a**; B(Et)	NaOH	24	**21c** (66), **37b** (20)
14	**18a**; B(i-Pr)	$Yb(OTf)_3$	49(7)[d]	**21d** (4), **37c** (61)
15	**18a**; B(i-Pr)	NaOH	4	**21d** (5), **37c** (78)
16	**18a**; **38a**	$Yb(OTf)_3$	4.5[e]	**21c** (13), **37b** (62.5)
17	**18a**; **38a**	$Yb(OTf)_3$	1	**21c** (16), **37b** (77)
18	**18a**; **38b**	$Yb(OTf)_3$	6[e]	**21e** (14.5), **37d** (59)
19	**18a**; 1-heptyne	$HgCl_2$ – $Yb(OTf)_3$	72	**21e** (3.2), **37d** (0.8)

[a]Yield of free base unless otherwise indicated.
[b]Yield of picrate.
[c]Time of addition of reagents to catalyst; see Experimental.
[d]Parentheses, reflux time in toluene; no parentheses, time at 95 °C; see Experimental.
[e]Room temperature reaction.

other absorptions, the NMR spectrum possessed peaks for eight aromatic hydrogens and three methylene groups at δ 2.78, 2.98, and 5.04 (coupled to the NH by 6.2 Hz). Four of the aromatic hydrogens had a splitting pattern identical to and chemical shifts (δ 6.68 (t), 6.90 (d), 7.35 (dt), 7.58 (dd)) similar to those found in 2-aminobenzaldehyde (20). The chemical shifts of the remaining aromatic hydrogens (δ 7.43 (t), 7.63 (d), 7.78 (d), 8.05 (s)) were essentially identical to those reported for H-6, H-7, H-5, and H-4, respectively, of quinoline (30), and the multiplicities were concordant with those expected for a 2,3,8-trisubstituted derivative. This substitution pattern was strongly supported by a ROESY experiment, which showed that the δ 2.78 methylene group was vicinal to the hydrogen at δ 8.05, that the two upfield methylene groups were also vicinal, and that the low field (δ 5.04) methylene moiety was vicinal to the δ 7.63 hydrogen. The above information is fully accommodated by the quinoline derivative with structure **25a** (Scheme 5). In particular, the unusual chemical shift of the methylene group at C-8 stems from the strong deshielding effect of the peri lone electron pair of the quinoline nitrogen atom. The formation of this compound clearly requires the involvement of one or more Schiff base intermediates.

When the above reaction was attempted with propanal under similar conditions (sealed vessel), only a miniscule amount (ca. 1.5%) of **25b** was formed (crystalline). The major product in this complex reaction mixture was a structurally different yellow-colored oily substance (see below). A reaction with acetaldehyde (4 equiv.) at reflux temperature gave a complex mixture containing no major product and no trace of a material with an *Rf* expected for **25c**. It was assumed that the failure to generate significant amounts of **25b,c** was connected with the volatility of the aldehydes; therefore, the reactions were carried out at room temperature. After 2 to 3 days, acetaldehyde (4 equiv.) gave a major, new, yellow-colored oil (ca. 65% yield), but no quinoline. This material had a mass spectral molecular weight of 294, i.e., derived from the condensation of two molecules of acetaldehyde with two molecules of **18a** minus two molecules of water ($C_{18}H_{18}N_2O_2$). The NMR spectrum of this apparently homogeneous material (TLC) indicated, however, that it was a 4:1 mixture of isomers. The major component showed signals for two aldehyde moieties (δ 9.86 and 9.81), two NH groups (δ 8.67 and 8.40), seven aromatic hydrogens, multiplets corresponding to four mutually coupled aliphatic protons (δ 4.86, 3.38, 2.31, and 1.71), and a methyl group attached to a secondary carbon atom. The hydrogens at δ 4.86 and 3.83 were also coupled to the low-field NH and the methyl group, respectively. Deuteration of the NH hydrogens and decoupling of the methyl group permitted measurement of all the aliphatic hydrogen coupling constants (Table 3) and assignment of the *cis* 2,4-disubstituted tetrahydroquinoline structure **26a** to this substance, with the methyl and aniline moieties occupying equatorial sites in a half-chair system. Full decoupling studies were not carried out on the minor component, but the data in Table 3 indicate that it is the *trans* stereoisomer **26b** with the anilino group axial. When propanal was used in the room temperature reaction, a not-readily-separable 54:34:12 mixture of stereoisomers was obtained in about 50% yield. The high-temperature reaction

Scheme 5.



mentioned above gave mainly the major isomer, and the NMR spectral data in Table 3 establish that this is the 2,3,4-trisubstituted tetrahydroquinoline **26c**, analogous to **26a** but with a C-3 axial methyl group. The isomers of intermediate and least abundance have structures **26d** and **26e**, with the 2,3,4-substituents arranged a,e,e and a,a,e. In addition to the three tetrahydroquinolines, the acyclic dialdehyde **27** was isolated as a single isomer in ca. 40% yield. The room-temperature reaction of 2-aminobenzaldehyde and phenylacetaldehyde was not studied in detail, but a very insoluble, surprisingly high-melting (236 °C) yellow solid could be isolated in ca. 15% yield. The NMR spectral data (Table 3) unequivocally show that this is the all-equatorial isomer **26f**.

The formation of tetrahydroquinolines from anilines and aliphatic aldehydes has been known for some time (31, 32) and proceeds via an intermediate Schiff base dimer **28**, which sometimes can be isolated (e.g., for X = H, R = Et, Ar = Ph (31)). The dimer cyclization is acid catalyzed, high yielding, and takes place at room temperature. It is apparent that the dialdehyde **27** is the hydrolysis product of the intermediate enroute to the tetrahydroquinolines **26**. It is also worth noting that the tetrahydroquinolines and the dihydroquinoline described below are well-recognized intermediates in the Doebner–Miller quinoline synthesis (see ref. 5, pp. 102–104).

The high-temperature ytterbium-triflate-promoted reaction of phenylacetaldehyde with 2-aminobenzaldehyde gave, in addition to 3-phenylquinoline, a complicated neutral mixture from which a crystalline, yellow-colored, structurally unique monoaldehyde could be isolated (13%–29%). That this substance was the 1,2-dihydroquinoline **29** was evident from its NMR spectrum, which showed, among other signals, absorptions for an aldehyde hydrogen, an NH moiety, an olefinic hydrogen (singlet), a methine hydrogen, and a benzylic methylene group at δ 9.77, 8.38, 6.61, 5.03, and 2.82, respectively. The methine hydrogen was coupled to both the NH (J = 2.6 Hz) and the methylene hydrogens (J = 6.0 Hz).

Solutions of **29** underwent slow aerial oxidation to the corresponding quinoline **30**, which was obtained much more efficiently by oxidation with Fremy's salt (33). The aldehyde hydrogen of the latter compound is found at δ 11.46, nearly δ 2 downfield from that observed for **29**. The remarkably low-field position of this proton must be a consequence of an aldehyde conformation in which the hydrogen and oxygen are close to and remote from the lone pair of the quinoline nitrogen atom, which is a conformation that the aldehyde must adopt to avoid an unfavorable dipole–dipole interaction. The hydrogen of a series of quinoline-8-carboxaldehydes has been reported to resonate at δ 11.3–11.5 without comment (34).

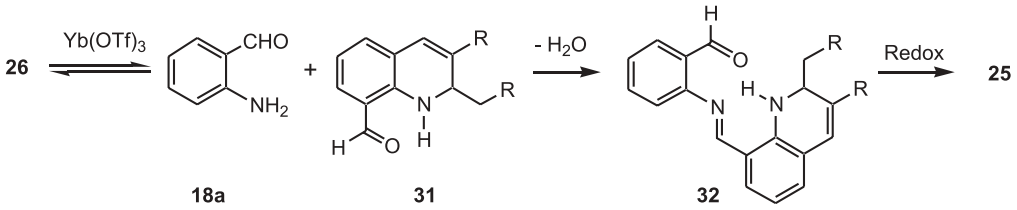
The isolation of the dihydroquinoline **29** was of considerable significance, because it suggested a plausible mechanism for the formation of the quinoline containing dimers **25**. Specifically, fragmentation of the tetrahydroquinoline dimers **26** to 2-aminobenzaldehyde and the 1,2-dihydroquinoline **31**, followed by Schiff base formation from these fragments, would generate **32**, which could lead to **25** by an intramolecular redox process (Scheme 6). In fact, a boiling solution of the isomeric tetrahydroquinolines **26c**, **26d**, and **26e** in toluene containing 10 mol% of ytterbium triflate was slowly (15–21 h) converted into a mixture from which the previously described quinoline dimer **25b** could be isolated in ca. 25% yield. The tetrahydroquinoline mixture derived from acetaldehyde (**26a** and **26b**) was converted even more rapidly (4 h) and more efficiently (>45% yield) into the 2-methyl analog **25c**.

Why are the Schiff bases derived from aliphatic aldehydes and 2-aminobenzaldehyde converted exclusively into tetrahydroquinolines at room temperature and only give the expected 3-substituted quinolines at higher temperature? The answer must certainly be associated with the geometry of the Schiff base. At ambient temperature, the thermodynamically more stable *E*-isomer **33** (Scheme 7) must be generated essentially exclusively. This geometry cannot, however, lead to the 3-substituted quinoline; therefore, intermolecular aldolization to the Schiff base dimers followed by cyclization to the tetrahydroquinoline derivatives takes place. At higher temperature the *E*-isomer exists in equilibrium

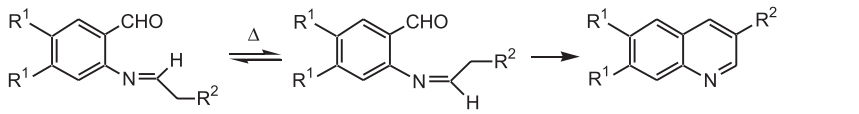
Table 3. NMR spectral data for tetrahydroquinolines **26** in CD_2Cl_2.

			δ (ppm) and *J* (Hz)											
Compound	R	Stereo	**1**-NH	**2**	**3a**	**3e**	**4**	**4**-NH	**2**-Me	**2**-$MeCH_2$	**2**-CH_2(A)	**2**-CH_2(B)	**3**-Me	CHO	CHO
26a	H	2e,4e	8.40	3.83 10.9 (2a,3a) 3.2 (2a,3e)	1.71 12.5 (3a,3e) 11.8 (3a,4a) 4.8 (3e,4a)	2.31	4.86 8.3 (4a,NH)	8.67	1.36 6.3 (2a,Me)					9.81	9.86 0.4
26b	H	2e,4a	8.37	3.60 10.1 (2a,3a) 3.1 (2a,3e)	1.65 13.1 (3a,3e) 3.6 (3a, 4e) 3.6 (3e, 4e)	2.17	4.74 7.2 (4e,NH)	8.48	1.33 6.5 (2a,Me)					9.78	9.84
26c	Me	2e,3a,4e	8.46	3.69 2.9 (2a,3e)		2.29 4.2 (3e,4a)	4.99 8.7 (4a,NH)	8.66		1.14 7.7	1.66 7.3 (2a,CH_2)		0.85 7.1	9.86	9.94
26d	Me	2a,3e,4e	8.56	3.30 3.4 (2e,3e)		1.91 10.4 (3a,4a)	4.45 9.2 (4a,NH)	8.64		1.07 7.6	1.60 14.1 (A,B) 3.4 (2e,CH_2)	1.86	1.06 7.0	9.87	9.92 0.8
26e	Me	2a,3a,4e	8.41	3.36 3.0 (2e,3e)	2.16 2.2 (3e,4a)		4.36 7.2 (4a,NH)	8.44		1.01 7.6	1.55 13.4 (A,B) 3.0 (2e,CH_2)	1.65	0.83 6.9	9.76 0.7	9.85
26f	Ph	2e,3e,4e	8.59	4.11 10.4 (2a,3a)	2.98 10.8 (3a,4a)		4.95 8.6 (4a,NH)	8.56			2.49 13.8 (A,B) 9.9 (2a,B) 3.0 (2a, A)	2.84		9.56 0.3	9.77

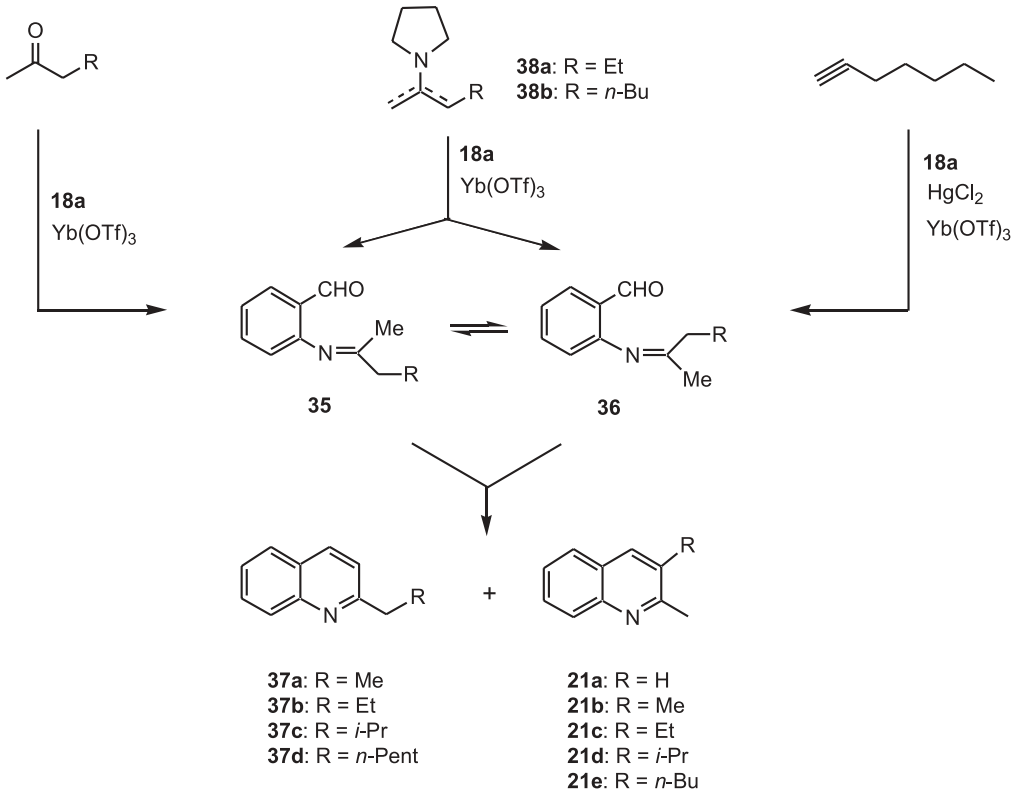
Scheme 6. Generation of quinolines **25** from tetrahydroquinolines **26**.



Scheme 7. Aldehyde Schiff base cyclization.



Scheme 8. Ketone Schiff base cyclization.



with *Z*-isomers **34**, which by an intramolecular aldolization can now produce the 3-alkylquinoline. The conversion of the tetrahydroquinoline derivatives **26** into the dimeric quinoline derivatives **25** must also involve higher energy processes, and thus, the temperature must be raised for this transformation to occur at a useful rate as well.

There are two important consequences of the above results. Firstly, given that the *Z*-Schiff base is a high-temperature intermediate, it should be possible to devise conditions that would favor its formation and thus increase the 3-alkylquinoline yield. Indeed, addition of a solution of the 2-aminobenzaldehydes **18a** or **18b** and a slight excess of *n*-heptanal or phenylacetaldehyde in toluene to a boiling suspension of ytterbium triflate in toluene over a 3 to 4 h period gave the expected 3-substituted quinolines in 40%–80% yields (Scheme 7 and Table 2, entries 7–10). Secondly, if Schiff bases of unsymmetrical ketones (e.g., methyl alkyl ketones) could be generated, and if *E–Z* equilibration did occur (e.g., **35** with **36**, Scheme 8), then mixtures of two quinolines (**21** and **37**) should be formed, and the 2-

substituted quinoline **37** might well predominate. This would be quite different from what occurs under the usual basic or acidic conditions of the Friedländer synthesis (see above). Schiff bases unfortunately do not form from ketones and 2-aminobenzaldehyde under the conditions described above for aldehydes. It was found, however, that heating a solution of **18a** in 2-butanone containing catalytic ytterbium triflate at 95 °C resulted in the very slow (>2 days) consumption of the aldehyde. Removal of the excess 2-butanone, followed by heating the residue in toluene at reflux temperature for 7 h, gave a 1.7:1 mixture of 2,3-dimethylquinoline (**21b**) and 2-ethylquinoline (**37a**, Scheme 8) in over 90% yield (Table 2, entry 11). In contrast, under alkaline conditions, 2,3-dimethylquinoline was the only product obtained (Table 1, entry 9). When 2-pentanone was used in the above reactions, 2-*n*-propylquinoline (**37b**) predominated over 2-methyl-3-ethylquinoline (**21c**) by a factor of 1.2 for ytterbium triflate, whereas the latter quinoline was the major product in the sodium-hydroxide-mediated reaction (**21c**:**37b** = 3.3:1, Table 2, entries 12 and 13). Hawes and Gorecki (35) also observed a slight predominance (factor of 1.1) of the kinetic over the thermodynamic product in the piperidine-catalyzed reaction of 4-aminonicotinaldehyde with neat 2-butanone. These results suggested that the kinetic product might be favored to an even greater extent for 4-methyl-2-pentanone, and a 15.3:1 **37c**:**21d** ratio supported this prediction. It was astonishing to find, however, that essentially the same product ratio (15.6:1) was observed for the sodium-hydroxide-promoted reaction, in which a Schiff base intermediate is unlikely based on the data described herein. Since the enolization of 4-methyl-2-pentanone occurs rapidly at both sites (deuteration complete in <5 min in perdeuteriomethanol containing a catalytic amount of the sodium derivative), it is probable that the highly selective formation of **37c** in the alkali-mediated condensation results from steric inhibition of aldolization at the methylene site. It is significant that analogous results have been reported for β-methyl substituted ketones both under acidic (36) and basic (37) conditions. Except for the case of 4-methyl-2-pentanone, the alterations in product ratios toward the kinetic one, although significant, are not so large that they are convincingly diagnostic of Schiff base intermediates. Since anhydrous conditions were not maintained in these reactions, it is quite possible that substantial amounts of the quinoline were formed by intermolecular aldol processes in both the piperidine- (35) and the ytterbium-triflate-catalyzed reactions. The facile acid-catalyzed transamination of enamines and Schiff bases (38–40) and the well-known water sensitivity of the latter prompted an examination of the reactivity of the pyrrolidine enamines of 2-pentanone (**38a**) and 2-heptanone (**38b**) towards 2-aminobenzaldehyde (Scheme 8). For example, a solution of **18a** in anhydrous toluene containing 2.4 equiv. of the enamine **38a** (1 equiv. of **38a** to ensure anhydrous conditions) and catalytic ytterbium triflate was rapidly and efficiently converted into a mixture of the expected quinolines **21c** and **37b**, both at reflux (<1 h) and room (4 h) temperature. The kinetic product **37b** was favored by a factor of ca. 5 in both cases (Table 2, entries 16 and 17). The kinetic product was also highly favored for the reaction of **18a** with the enamine **38b** at room temperature (**37d**:**21e** = 4:1). These are reasonable results if both the generation of the Schiff bases (mainly **35**) and the cyclization thereof to the quinolines are very fast processes.

Lastly, the room-temperature hydroarylamination of 1-heptyne with **18a** in the presence of an equimolar amount of mercuric chloride (41) and catalytic ytterbium triflate gave a mixture of **37d** and **21e** (4:1) in low, but reproducible yield (4%). In this case, the quinolines must be generated via Schiff base intermediates. The 4:1 kinetic:thermodynamic product ratio was identical to that observed for **38b** and strongly supports Schiff base intermediates in the enamine based reactions.

When this study was completed, Dormer et al. (37) reported that the kinetic product was dramatically favored when the methyl alkyl ketone was added slowly to a hot ethanolic solution of the 2-aminoarylaldehyde, a slight excess of various secondary amines, and a catalytic amount of sulfuric acid. Kinetic:thermodynamic product ratios as high as 24 were observed when the secondary amine was 1,3,3-trimethyl-6-azabicyclo[3.2.1]octane (TABO). The authors did not offer an explanation of these remarkable results. It is our contention that the reaction conditions reported by these investigators are precisely those that should result in the rapid formation and cyclization of the kinetic Schiff base, which arises by the fast transamination of an intermediate enamine.

In conclusion, the results described herein show that the generation of quinolines from simple aldehydes and 2-aminobenzaldehydes under the typically used acidic or basic conditions of the Friedländer synthesis takes place by a process in which an intermolecular aldol condensation is the first step. It is highly probable that the same mechanism is involved when 2-aminoarylketones are used to prepare quinolines. When Schiff bases are deliberately generated from aldehydes at room temperature, the kinetically formed *E*-isomer is diverted to nonFriedländer products. 3-Substituted quinolines are formed only at higher temperatures, which effect isomerization of the *E*-Schiff base to the *Z*-isomer, which then undergoes intramolecular aldolization to the heterocyclic aromatic product. When Schiff bases are generated from methyl alkyl ketones, the kinetically favored, less-hindered *Z*-Schiff base is formed preferentially and rapidly cyclizes to the 2-alkylquinoline derivative. Thus, the hallmark of such cyclizations is a high kinetic:thermodynamic product ratio, a result completely opposite to that observed when the usual acidic or basic reaction conditions are employed in the Friedländer quinoline synthesis. This result has obvious synthetic consequences, which have been convincingly demonstrated in the recently described study of Dormer et al. (37).

Experimental

General

The melting points are uncorrected. The NMR spectra (300 and 600 MHz) were recorded in deuteriochloroform unless indicated otherwise, and the chemical shifts are reported in parts per million (ppm) (δ) with internal tetramethylsilane as zero. The IR spectra were measured as dispersions in KBr for solids and as films for liquids. The UV spectra were taken in methanol solution. Reactions were followed by TLC on silica gel plates unless otherwise indi-

cated. Column chromatographic separations were effected using 230–400 mesh silica gel. The columns were packed dry, successively layered with the crude reaction mixture (absorbed onto silica gel) and a small amount of sand, and then eluted with the appropriate solvent system. The mixtures absorbed on silica gel were prepared by dissolving the reaction mixture in dichloromethane, adding this solution to silica gel, and then removing the solvent in vacuo.

The terms "worked up in the usual manner", "the usual workup", etc., signify that the extract was dried over anhydrous sodium sulfate, and the solvent was then removed in vacuo.

4-Hydroxy-4-(2-azidophenyl)-2-butanone (14c) and 4-(2-azidophenyl)-(3*E*)-buten-2-one (16c)

Aqueous sodium hydroxide (0.25 mol L^{-1}, 0.6 mL) was added dropwise at 15 °C to a stirred solution of 2-azidobenzaldehyde (**13b** (42)) (294 mg, 2 mmol) dissolved in a mixture of acetone (2.6 mL), water (2 mL), and ethanol (2 mL). One half hour after the addition was completed, the reaction mixture was poured into aqueous sodium chloride and extracted with dichloromethane. The extract was washed with water and then worked up as usual to give an oil (401 mg), which was taken up in a small amount of dichloromethane and added to silica gel (2 g), and the mixture was evaporated to dryness in vacuo. This material was layered onto a dry packed column (3.5 × 8.5 cm) of silica gel (40 g) covered with sand and eluted with hexane – ethyl acetate ((70:30), 20 mL fractions (F)). F 2–4 contained the enone **16c** (34 mg, 9.1%), and F 6–10 contained the β-ketol **14c** (324 mg, 78.9%), both of which were crystalline.

After crystallization from cyclohexane and drying in vacuo at 23 °C for 5 h with protection from light, the β-ketol **14c** had mp 69 to 70 °C. ^{1}H NMR δ: 2.20 (s, 3H), 2.72 (dd, 1H, *J* = 9.5, 17.6 Hz), 2.91 (dd, 1H, *J* = 2.7, 17.6 Hz), 3.47 (d, 1H, *J* = 3.1 Hz, exchanged with D_2O), 5.34 (m, 1H), 7.13 (dd, 1H, *J* = 1.0, 8.0 Hz), 7.17 (td, 1H, *J* = 1.1, 7.7 Hz), 7.32 (td, 1H, *J* = 1.7, 7.7 Hz), 7.54 (dd, 1H, *J* = 1.6, 7.7 Hz). ^{13}C NMR δ: 30.62, 50.45, 65.31, 117.87, 125.18, 128.65, 133.83, 136.05, 209.22. Anal. calcd. for $C_{10}H_{11}N_3O_2$: C 58.94, H 5.40, N 20.48; found: C 58.85, H 5.40, N 20.60.

After crystallization from cyclohexane and drying in vacuo (17 h), the enone **16c** had mp 107 to 108 °C. ^{1}H NMR δ: 2.39 (s, 3H), 6.70 (d, 1H, *J* = 16.5 Hz), 7.15 (d, 1H, *J* = 7.8 Hz), 7.20 (td, 1H, *J* = 1.0, 8.1 Hz), 7.43 (td, 1H, *J* = 1.5, 8.5 Hz), 7.6 (dd, 1H, *J* = 1.5, 7.8 Hz). ^{13}C NMR δ: 27.20, 118.82, 125.05, 126.11, 127.90, 128.71, 131.54, 137.62, 139.32, 198.57. Anal. calcd. for $C_{10}H_9N_3O$: C 64.16, H 4.85, N 22.45; found: C 64.54, H 4.89, N 22.33.

4-(2-Nitrophenyl)-3-methyl-(3*E*)-buten-2-one (16b)

Sodium hydroxide (0.25 mol L^{-1}) was added dropwise at 15 °C to a stirred solution of 2-nitrobenzaldehyde (**13a**, 3.022 g, 20 mmol) in a mixture of 2-butanone (32 mL, 25.7 g), ethanol (12 mL), and water (20 mL), until the solution was weakly alkaline (ca. 15 mL). After 1 h the solution was diluted with water, and the mixture was extracted with ether, washed with saturated NaCl solution, and then processed as usual to give a mixture of the β-ketols **14b** and **15** (4.42 g). This mixture was dissolved in acetic anhydride (10 mL); sodium acetate (1.64 g, 20 mmol) was added, and the mixture was heated at reflux temperature for 1 h. Water was added cautiously to the hot solution to decompose the excess acetic anhydride, and when the vigorous reaction was over, the mixture was poured into ice-water and extracted with dichloromethane. The extract was washed successively with 10 wt % sodium carbonate solution and water and then worked up as usual. The crude product (4.07 g) was absorbed onto silica gel (20 g), loaded onto a dry packed column (6 × 28 cm) of silica gel (380 g), and eluted with hexane – ethyl acetate (70:30, 50 mL fractions). F 13–16 contained the desired crystalline enone **16b** (2.66 g, 65.6%). Subsequent fractions contained a mixture of **16b** and 5-(2-nitrophenyl)-(4*E*)-penten-3-one. An analytical specimen of the desired enone was obtained by crystallization from hexane and had mp 59 to 60 °C after drying in vacuo (4 h). ^{1}H NMR δ: 1.83 (d, 3H, *J* = 1.4 Hz), 2.50 (s, 3H), 7.39 (d, 1H, *J* = 7.8 Hz), 7.54 (td, 1H, *J* = 1.2, 7.8 Hz), 7.69 (td, 1H, *J* = 1.2, 7.5 Hz), 7.81 (bs, 1H), 8.18 (dd, 1H, *J* = 1.3, 8.2 Hz). ^{13}C NMR δ: 13.25, 26.26, 125.38, 129.58, 131.68, 132.30, 133.83, 136.64, 139.22, 147.88, 200.14. Anal. calcd. for $C_{11}H_{11}NO_3$: C 64.38, H 5.40, N 6.83; found: C 64.52, H 5.33, N 6.95.

Reduction of nitro compounds with iron powder and ammonium chloride

The following is a typical reduction. A mixture of the nitro compound (10 mmol) dissolved in ethyl acetate (100 mL), water (60 mL), iron powder (2.1 g, 37.5 mmol (Fisher Scientific, electrolytic, <100 mesh; iron powder from other suppliers, e.g., Malinckrodt, gave similar results, but the reductions were slower.)), and ammonium chloride (3.34 g, 62.5 mmol) was stirred vigorously at room temperature for the time period shown below. The mixture was filtered through Celite, and the inorganic residue was washed well with ethyl acetate. The ethyl acetate phase was separated and combined with an ethyl acetate extract of the aqueous phase; the extract was washed with saturated NaCl solution and then worked up as usual. The crude product was then purified by column chromatography on silica gel as described below.

4-(2-Aminophenyl)-(3*E*)-buten-2-one (17a)

Reaction time, 17 h. A 4 mmol scale reaction product (absorbed on silica gel, 3 g) was purified by column (3.5 × 14 cm) chromatography on silica gel (67 g, 25 mL fractions). The product (0.516 g, 80.0%), present in F 3–5, was obtained as a yellow oil. ^{1}H NMR δ: 2.36 (s, 3H), 4.01 (bs, 2H), 6.53 (d, 1H, *J* = 16.0 Hz), 6.71 (dd, 1H, *J* = 1.3, 8.3 Hz), 6.77 (td, 1H, *J* = 1.0, 7.3 Hz), 7.18 (td, 1H, *J* = 1.5, 7.3 Hz), 7.39 (dd, 1H, *J* = 1.5, 8.0 Hz), 7.68 (d, 1H, *J* = 16.0 Hz). ^{13}C NMR δ: 28.47, 117.30, 119.48, 120.29, 127.16, 128.57, 131.96, 139.06, 146.32, 198.63. A sample of this material was converted into the pivalamide (59.9%) by the technique described below for **17b**. A sample on solution in hot toluene and dilution with an equal volume of hexane gave material with mp 119 to 120 °C (lit. (43) value mp 117 to 118 °C).

4-(2-Aminophenyl)-3-methyl-(3*E*)-buten-2-one (17b)

Reaction time, 20 h. The crude product from an 8.38 mmol reaction was absorbed onto silica gel (8 g) and

purified on a column (4 × 23 cm) of silica gel (152 g) using hexane – ethyl acetate (65:35, 50 mL fractions). The product was contained in F 10–15 as an oil (1.266 g, 83.8%). IR (film) (cm^{-1}): 3452, 3366, 3244, 1659, 1623. ^{1}H NMR δ: 1.95 (d, 1H, J = 1.4 Hz), 2.46 (s, 3H), 3.74 (bs, 2H), 6.74 (dd, 1H, J = 0.9, 8.0 Hz), 6.80 (dt, 1H, J = 1.0, 7.5 Hz), 7.12 (dd, 1H, J = 1.6, 7.6 Hz), 7.17 (dd, 1H, J = 1.5, 7.7 Hz), 7.45 (bs, 1H). ^{13}C NMR δ: 13.64, 26.38, 116.20, 118.77, 121.84, 130.02, 130.11, 136.19, 144.70, 200.55.

The pivalamide of this compound was prepared as follows. Trimethylacetyl chloride (0.25 mL, 245 mg, 2.03 mmol) was added all at once to a stirred solution of the above amino compound (269 mg, 1.49 mmol) in toluene (30 mL) containing triethylamine (0.3 mL, 218 mg, 2.15 mmol) and 4-dimethylaminopyridine (18 mg) at 0 °C. The cooling bath was removed, and the mixture was stirred at room temperature for 18 h. The mixture was washed successively with water, 1 mol L^{-1} HCl, 10 wt % sodium carbonate, and saturated NaCl solution. After the usual workup, the brown solid was taken up in hot toluene (3 mL) and diluted with hexane (9 mL) to give the pivalamide (127 mg, mp 111 to 112 °C). A second crop (31 mg, mp 110–111.5 °C, total yield, 158 mg, 40.9%) of product was obtained from the mother liquor. Recrystallization of the first crop gave the analytical specimen, which had mp 111.5–112 °C, after drying in vacuo (9 h at 40 °C). Anal. calcd. for $C_{16}H_{21}NO_2$: C 74.10, H 8.16, N 5.40; found: C 74.33, H 8.10, N 5.57.

2′-Aminocinnamaldehyde (17c)

Reaction time, 4 h. After washing the ethyl acetate solution of the crude product with saturated NaCl solution and drying over sodium sulfate, the solvent was removed in vacuo at room temperature or below and the amino compound (100% yield) was immediately dissolved in toluene. Toluene solutions of this material, which contains a trace of quinoline (TLC), can be kept for a few days without significant decomposition when stored at 5 °C with protection from light.

2-Aminobenzaldehyde (18a)

Reaction time, 5 h. The crude product from a 20 mmol reaction was purified by normal column (4.2 × 18 cm) chromatography on silica gel (125 g), using hexane – ethyl acetate (70:30, 50 mL fractions). F 5–8 contained the product (2.08–2.25 g, 86%–93%), which crystallized spontaneously and usually had mp 37 to 38 °C (lit. (19) value mp 38 to 39 °C) after drying in vacuo. It is indefinitely stable when stored at 5 °C.

2-Amino-4,5-dimethoxybenzaldehyde (18b)

Reaction time, 20 h. The crude product from a 10 mmol reaction was purified by normal column (3.5 × 19.5 cm) chromatography on silica gel (100 g) using hexane – ethyl acetate (1:1, 50 mL fractions). F 7–13 contained the product (1.395 g, 77%), which had mp 82–84 °C (lit.(44) value mp 86 °C) after drying in vacuo. ^{1}H NMR δ: 3.85 (s, 3H), 3.89 (s, 3H), 6.12 (s, 1H), 6.88 (s, 1H), 9.69 (d, 1H, J = 0.4 Hz). ^{13}C NMR δ: 56.36, 56.92, 98.82, 111.75, 116.43, 141.42, 147.67, 156.56, 191.78.

Preparation of 2-methylquinoline-*N*-oxide (20) and 2-methylquinoline (21a) from the β-ketol 14a

Iron – ammonium chloride reduction

This reduction was effected in the manner described above on a 1 mmol scale. Evaporation of the ethyl acetate phase in vacuo gave 92 mg of a crystalline solid. The aqueous phase was brought to pH 9 with solid sodium carbonate, then saturated with sodium chloride and extracted with ethyl acetate. The extract was processed as usual to give a further 42 mg of solid. The solid material was identical to authentic **20** (yield 75.6%) and contained only a trace of **21a** by TLC.

Catalytic reduction

A solution of **14a** (418 mg, 2 mmol) in ethanol (30 mL), containing 10% Pd–C (40 mg), was hydrogenated at room temperature and atmospheric pressure. After 25 min, hydrogen absorption (89% of theory) ceased, the mixture was filtered through Celite, and the solvent was removed in vacuo to give a residue (321 mg), which by ^{1}H NMR was an 80:20 mixture of **20** and **21a**. Crystallization from hot water gave the monohydrate of **20** (222 mg, 62.6%), which had mp 72.5–74 °C (lit. (45) value mp 77 to 78 °C).

Preparation of 2-methylquinoline (21a) from the azido compound 14c

Iron – ammonium chloride reduction

This reduction was carried out using the same reagent and solvent ratios as described above for the nitro compound reductions. Reaction time, 22 h. The ethyl acetate phase, containing **21a**, was extracted with 1 mol L^{-1} HCl; the acid extract was brought to pH 9 with solid sodium carbonate; the mixture was extracted with ethyl acetate, and the extract was washed with saturated NaCl solution. After the usual workup, the crude base (138 mg from a 1 mmol reaction) was converted into the picrate (317 mg, 85.1%) with picric acid (240 mg) in hot ethanol (10 mL). The picrate was identical to an authentic specimen by mmp, and the free base recovered therefrom was identical by NMR spectroscopy to authentic material.

Triphenylphosphine

A solution of the azido compound **14c** (61.5 mg, 0.3 mmol) in toluene (10 mL), containing triphenylphosphine (79 mg, 0.3 mmol), was stirred at room temperature. By 1 h, **21a** and triphenylphosphine oxide were clearly visible by TLC (20:80 ethyl acetate – hexane, UV), but no other new spots were present. After 2 h, the solution was heated at reflux temperature for 2 h; it was extracted with 1 mol L^{-1} HCl, and the acid extract was worked up exactly as described for the iron – ammonium chloride reduction. Crude **21a** (41 mg) was converted into the picrate (81.7 mg, 73.3%) with picric acid (70 mg) in hot ethanol (4 mL).

Preparation of the quinolines by isomerization of 17a-c

With sodium hydroxide

2-Methylquinoline (21a)

A solution of **17a** (100 mg, 0.62 mmol) in ethanol (3 mL), water (1 mL), and 1 mol L^{-1} NaOH (0.1 mL) was stirred at room temperature for 22 h. Water was added, and the mix-

ture was extracted with ethyl acetate; the extract was washed with saturated NaCl solution and worked up in the usual way. The crude base (96 mg) was converted into the picrate (192 mg, 83.4%) in the usual way.

Quinoline

A solution of the freshly prepared enal **17c** (147 mg, 1 mmol) in ethanol (6 mL), water (2 mL), and 1 mol L^{-1} NaOH (0.1 mL) was left at room temperature. Additional NaOH was added at 22 h (1 mol L^{-1}, 0.2 mL) and at 47 h (2.5 mol L^{-1}, 0.2 mL). After 75 h the ethanol was removed in vacuo, and the residue was made acidic with 1 mol L^{-1} HCl and washed with ethyl acetate. The acidic phase was then worked up, as described for the preparation of **21a** from **14c** above. The crude base was converted into quinoline picrate (224 mg, 62.5%).

2,3-Dimethylquinoline (21b)

A solution of the enone **17b** (120 mg, 0.67 mmol) in ethanol (3 mL), water (1 mL), and 1 mol L^{-1} NaOH (2.2 mL) was heated at reflux temperature for 16 h. The reaction mixture was worked up as described above for the preparation of **21a**. The crude base was converted into the picrate (213 mg, 82.8%). A sample of the picrate was stirred with excess 1 mol L^{-1} NaOH and toluene. The toluene phase was separated, washed with saturated NaCl solution, and worked up in the usual way to give 2,3-dimethylquinoline, mp 67–68.5 °C (lit. (46) value mp 68.2–69 °C).

Acid-mediated isomerization

2-Methylquinoline (21a): 1.5 mol L^{-1} HCl

A solution of **17a** (100 mg, 0.62 mmol) in dioxan (3 mL) and 3 mol L^{-1} HCl (3 mL) was heated at reflux temperature for 1 h. The cooled solution was diluted with water and made basic with solid sodium carbonate. The mixture was extracted with ethyl acetate; the extract was washed with saturated NaCl solution and worked up in the usual way to give the crude base (86 mg), from which was obtained the picrate (189 mg, 81.8%).

2-Methylquinoline (21b): Catalytic sulfuric acid in acetic acid

To a solution of the enone **17a** (315 mg, 1.95 mmol) in acetic acid (8 mL) was added a 0.18 mol L^{-1} solution of sulfuric acid in acetic acid (2 mL), and the blood-red reaction mixture was heated at reflux temperature for 2.25 h. Toluene was added, and the mixture was evaporated to a small volume in vacuo. The residue was diluted with water, made basic with sodium carbonate, and extracted with ethyl acetate. The extract was washed with 1 mol L^{-1} HCl, and the acid phase was made basic with solid sodium carbonate and extracted with ethyl acetate. The extract was washed with saturated NaCl solution and worked up as usual to give an oil (219 mg), which was absorbed onto silica gel (2.2 g) and purified by column (2.2 × 12 cm) chromatography on silica gel (23 g) using hexane – ethyl acetate (65:35, 10 mL fractions). F 6–9 contained the product (168 mg), which was converted into the picrate (251 mg, 34.6%).

2,3-Dimethylquinoline (21b): 1.5 mol L^{-1} HCl

The enone **17b** was converted into **21b** exactly as described above to give the picrate in 86.7% yield.

Preparation of the quinolines from 2-aminobenzaldehyde (18a) and ketones

Sodium-hydroxide-mediated condensations

2-Methylquinoline (21a)

A solution of **18a** (121 mg, 1 mmol) in ethanol (4 mL), water (4 mL), acetone (0.6 mL, 0.475 g, 8 mmol), and 1 mol L^{-1} NaOH (0.2 mL) was left at room temperature for 47 h. The reaction mixture was worked up exactly as described for the preparation of **21a** from **17a** under alkaline conditions to give the picrate (298 mg, 80.0%).

2,3-Dimethylquinoline (21b)

A solution of **18a** (121 mg, 1 mmol) in ethanol (6 mL) and 1 mol L^{-1} NaOH (3.5 mL) containing 2-butanone (108 mg, 1.5 mmol) was left at room temperature for 12 h and then worked up as described above for **17a**. The crystalline base was converted into the picrate (296 mg, 76.6%).

Acid-mediated condensation

2-Methylquinoline (21a)

To a solution of **18a** (61 mg, 0.5 mmol) and acetone (87 mg, 1.5 mmol) in acetic acid (4.5 mL) was added a 0.18 mol L^{-1} solution of sulfuric acid in acetic acid (0.5 mL), and the solution was heated at reflux temperature for 18 h. The reaction mixture was worked up exactly as described for the sulfuric-acid-catalyzed isomerization of **17a**. The crude product (43 mg) was absorbed onto silica gel (1 g) and purified by column (1.8 × 5.5 cm) chromatography on silica gel (9 g) using hexane – ethyl acetate (60:40, 10 mL fractions). F 2–4 contained the product (20 mg), which was converted into the picrate (49 mg, 26.2%).

2-Methylquinoline (21a) by photolysis of 17a

A solution of the enone **17a** (20 mg, 0.124 mmol) in ethanol (4 mL) in a pyrex test tube was placed next to a Pen-Ray Model PS-1 pencil light, and both were enveloped in aluminum foil. The solution was irradiated until TLC showed that **17a** was absent (24 h); the solvent was removed in vacuo, and the crude base was converted into the picrate (34.4 mg, 74.6%).

Preparation of 3-substituted quinolines 24a-c from 18a and aldehydes

p-Toluenesulfonic acid catalyst

A solution of **18a** (121 mg, 1 mmol) and the appropriate aldehyde (1.2 mmol, freshly liberated from the bisulfite adduct) in toluene (50 mL) containing *p*-toluenesulfonic acid monohydrate (10 mg) was heated at reflux temperature with separation of water in a Dean–Stark apparatus until **18a** was no longer present by TLC (see Table 2). The base was extracted into 1 mol L^{-1} HCl; the extract was made basic with solid sodium carbonate and extracted with ethyl acetate. After the usual processing the crude base was converted into the known picrate (See Table 2 for yields). The bases, liberated from the picrates, were also fully characterized by NMR spectroscopy.

Ytterbium triflate as catalyst

Normal conditions

A solution of **18a** (121 mg, 1 mmol) and the appropriate aldehyde (1.2–1.4 mmol, freshly liberated from the bisulfite adduct) in toluene (10 mL) containing suspended ytterbium triflate (62 mg, 0.1 mmol) was stirred at reflux temperature (argon atmosphere) for 4 h. The cooled mixture was vigorously stirred with 10 wt % sodium carbonate solution for 15 min, and the toluene phase was separated. The bases were extracted into 1 mol L^{-1} HCl and processed as described above. See Table 2 for picrate yields. When the product was 3-phenylquinoline, HCl extraction often caused the insoluble salt to crystallize and form an emulsion. In this case, it was necessary to alternatively extract with HCl and water, until all of the salt had been removed.

*Modified conditions: Preparation of quinolines **24a** and **24c-e***

A solution of **18a** or **18b** (2 mmol) and the aldehyde (2.4–2.5 mmol) in toluene (15 mL) was added dropwise (argon atmosphere) to a stirred suspension of ytterbium triflate (124 mg, 0.2 mmol) in toluene (15 mL) at reflux temperature over the time period indicated in Table 2 in parentheses. Heating at reflux temperature was then continued until the total elapsed time indicated in Table 2. The cooled mixture was vigorously stirred with 10 wt % sodium carbonate solution for 15 min, and the toluene phase was separated. The subsequent workup depended on the specific compound. For **24a** and **24c**, the bases were extracted with 1 mol L^{-1} HCl and liberated with sodium carbonate as described above. The yield of **24a** corresponds to that of the picrate, whereas that of **24c** refers to the free base. See below for **24d** and **24e**.

3-*n*-Pentyl-6,7-dimethoxyquinoline (24d)

The acid extract was made basic in the usual way and extracted with ethyl acetate. The extract was washed with saturated NaCl solution and then processed as usual to give the crude crystalline base (277 mg). This material was absorbed onto silica gel (1.5 g) and subjected to column (3.5 × 11.5 cm) chromatographic purification on silica gel (55.5 g) using 1:1 hexane – ethyl acetate (25 mL fractions). F 10–13 contained the solid product (217 mg, 41.8%). After two crystallizations from hexane and drying in vacuo for 24 h, it had mp 63.5–65 °C. ^{1}H NMR δ: 0.90 (t, 3H, J = 7.0 Hz), 1.29–1.40 (m, 4H), 1.65–1.75 (m, 2H), 2.74 (t, 2H, J = 7.6 Hz), 4.01 (s, 3H), 4.02 (s, 3H), 7.00 (s, 1H) 7.40 (s, 1H), 7.71 (d, 1H, J = 2.1 Hz), 8.57 (d, 1H, J = 2.1 Hz). ^{13}C NMR δ: 14.01, 22.51, 31.01, 31.37, 33.06, 56.00, 56.06, 104.78, 107.81, 123.72, 132.73, 133.68, 143.61, 149.58, 149.79, 151.71. Anal. calcd. for $C_{16}H_{21}NO_2$: C 74.10, H 8.16, N 5.40; found: C 74.25, H 8.16, N 5.56.

3-Phenyl-6,7-dimethoxyquinoline (24e)

The toluene solution containing the reaction mixture was not extracted with acid. Instead, after washing with saturated NaCl solution and the usual workup, the crude product from a 1 mmol reaction was absorbed onto silica gel (1.5 g) and subjected to column (2.2 × 20 cm) chromatographic purification on silica gel (35.5 g) using 1:1 hexane – ethyl acetate (20 mL fractions). F 9–18 contained the product (208 mg, 78.4%), the ^{1}H NMR spectrum of which was identical to that reported (47).

2-*n*-Hexyl-3-*n*-pentyl-8-(2-formyl)anilinomethylquinoline (25a)

A 2 mmol reaction was carried out as described in the section Normal conditions above, except that the acid extraction to remove **24a** was not carried out. The toluene solution of the product mixture was washed with saturated NaCl solution and then worked up as usual to give an oil (439 mg), which was absorbed onto silica gel (2.2 g) and subjected to column (3.5 × 17 cm) chromatography on silica gel (88 g) using hexane – ethyl acetate (90:10, 25 mL fractions). F 5–7 contained **25a** (104–179 mg, 25%–43%) as a yellow oil. IR: see Discussion section. UV (nm): 385 (ε 6520), 319.5 (ε 4620), 306.5 (ε 4330), 261.5 (ε 10 100), 229 (ε 57 700), 213 (ε 59 600). ^{1}H NMR: see Discussion section. ^{13}C NMR (CD_2Cl_2) δ: 14.58, 14.69, 23.34, 23.48, 28.93, 29.25, 30.20, 32.58, 32.71, 33.00, 36.12, 43.39, 112.23, 115.47, 119.49, 125.88, 126.85, 127.00, 127.92, 135.32, 136.27, 136.45, 137.31, 162.00, 194.50. MS m/z (%): 417 ([M + H]$^+$, 56), 312 (65), 296 (100), 212 (28), 198 (31), 171 (27). HR-FAB$^+$-MS m/z calcd. for $[C_{28}H_{36}N_2O]H^+$: 417.2897; found: 417.2895.

2-Ethyl-3-methyl-8-(2-formyl)anilinomethylquinoline (25b)

A mixture of the isomeric tetrahydroquinolines **26d-e** (227 mg, 0.704 mmol, see below for synthesis) in toluene (25 mL) containing suspended ytterbium triflate (48 mg, 0.077 mmol) was stirred at reflux temperature under argon for 22 h. The reaction mixture was stirred with sodium carbonate for 15 min, and then the toluene phase was processed as described above to give a solid residue (206 mg), which was absorbed onto silica gel (1.0 g) and purified by column (3.5 × 14 cm) chromatography on silica gel (69 g) using hexane – ethyl acetate (85:15, 20 mL fractions). F 3–5 contained the product (76 mg), and F 7 contained the product admixed with a slightly more polar material (8 mg). The major fraction on crystallization from cyclohexane gave the crystalline product in two crops, mp 145–147 °C (47 mg) and mp 144–146 °C (2 mg). The minor fraction gave an additional 2 mg of product, mp 144.5–145 °C, from cyclohexane. Total yields, 51 mg (23.8%). Recrystallization from cyclohexane gave an analytical specimen that had mp 147–148.5 °C after drying in vacuo (45 °C, 16 h). IR (KBr) (cm^{-1}): 3434, 3334, 2750, 1656. UV (nm): 386 (ε 6250), 318.5 (ε 3750), 304.5 (ε 3530), 263 (ε 9370), 228 (ε 51 600), 211 (ε 55 500). ^{1}H NMR (CD_2Cl_2) δ: 1.45 (t, 3H, J = 7.4 Hz), 2.48 (d, 3H, J = 0.9 Hz), 3.02 (q, 2H, J = 7.4 Hz), 5.16 (bs, 2H), 6.65 (td, 1H, J = 0.9, 6.7 Hz), 6.83 (d, 1H, J = 8.5 Hz), 7.30 (td, 1H, J = 1.7, 7.8 Hz), 7.37 (d, 1H, J = 7.1 Hz), 7.47 (dd, 1H, J = 1.7, 7.8 Hz), 7.57 (dd, 1H, J = <1, >6 Hz), 7.65 (dd, 1H, J = <1, 8.3 Hz), 7.85 (bs, 1H), 8.98 (bs, 1H, exchanged with D_2O), 9.83 (d, 1H, J = 0.6 Hz). ^{13}C NMR δ: 12.29, 19.40, 29.55, 43.22, 125.67, 126.39, 126.51, 127.59, 130.03, 135.82, 136.06, 137.02, 144.86, 151.47, 162.36, 194.25. Anal. calcd. for $C_{20}H_{20}N_2O$: C 78.92, H 6.62, N 9.20; found: C 79.25, H 6.58, N 9.35.

2-Methyl-8-(2-formyl)anilinomethylquinoline (25c)

A solution of a mixture of **26a** and **26b** (203 mg, 0.69 mmol, see below for synthesis) in toluene (20 mL) containing suspended ytterbium triflate (86 mg) was stirred at reflux temperature (argon atmosphere) for 4 h and then

worked up as described for **25b**. The crude product (177 mg) was absorbed onto silica gel (1 g) and subjected to column (3.5 × 11.5 cm) chromatographic purification on silica gel (54 g) using hexane – ethyl acetate (85:15, 20 mL fractions). F 5–10 contained the product (121 mg), which was crystallized from cyclohexane to give the desired material in two crops, mp 95–95.5 °C (85 mg) and mp 94.5–95 °C (10 mg). Thus the yield of **25c** was 95 mg (46.5%). Recrystallization of a sample from cyclohexane gave the analytical specimen, which had mp 94.5–95.5 °C after drying in vacuo (9.5 h). IR (KBr) (cm^{-1}): 3480 (bw), 3350, 2738, 1666. UV (nm): 383 (ε 6850), 317 (ε 3530), 304 (ε 3500), 267 (ε 9980), 224 (ε 52 900), 208 (ε 51 900), 206.5 (ε 52 500). ^{1}H NMR δ: 2.78 (s, 3H), 5.17 (d, 2H, *J* = 5.9 Hz), 6.65 (td, 1H, *J* = 0.8, 7.4 Hz), 6.76 (d, 1H, *J* = 8.5 Hz), 7.29 (td, 1H, *J* = 1.6, 8.6 Hz), 7.38 (t, 3H, *J* = 7.6 Hz), 7.47 (dd, 1H, *J* = 1.6, 7.7 Hz), 7.61 (dd, 1H, *J* = 1.0, 7.1 Hz), 7.66 (d, 1H, *J* = 8.1 Hz), 8.02 (d, 1H, *J* = 8.4 Hz), 9.02 (bs, 1H, exchanged with D_2O), 9.87 (s, 1H). ^{13}C NMR δ: 25.93, 43.21, 111.99, 115.19, 119.08, 122.37, 125.71, 126.82, 127.14, 127.42, 135.95, 136.09, 137.03, 146.30, 151.41, 158.68, 194.32. Anal. calcd. for $C_{18}H_{16}N_2O$: C 78.23, H 5.84, N 10.14; found C 78.50, H 5.89, N 10.22.

Synthesis of the tetrahydroquinolines 26

A solution of **18a** (242 mg, 2 mmol) and the appropriate aldehyde (8 mmol) in toluene (20 mL) containing suspended ytterbium triflate (124 mg, 0.2 mmol) was stirred at room temperature under argon for the time period indicated below. The reaction mixture was then vigorously stirred with excess 10 wt % sodium carbonate solution for 15 min; the toluene phase was separated, washed with saturated NaCl solution, and worked up as usual. The bases were purified as described below.

cis- And *trans*-2-methyl-4-(2-formyl)anilino-1,2,3,4-tetrahydroquinoline-8-carboxaldehydes 26a and 26b

The crude product from a 2 mmol reaction was absorbed onto silica gel (1.5 g) and purified by column (3.5 × 12.5 cm) chromatography on silica gel (63.5 g) using hexane – ethyl acetate (80:20, 25 mL fractions). F 4–7 contained the product as a TLC homogeneous oil (191–210 mg, 65%–72%), which by ^{1}H NMR spectroscopy was a 4:1 mixture of **26a** and **26b**. IR (film) (cm^{-1}): 3317, 2744, 1653. UV (nm): 388 (ε 12 000), 262.5 (ε 11 400) 237 (ε 33 800). ^{1}H NMR: see Table 3. ^{13}C NMR (*e*,*e*-isomer **26a**) δ: 22.51, 36.34, 46.93, 49.57, 111.39, 115.05, 115.84, 117.59, 118.99, 123.35, 132.40, 135.84, 136.48, 137.41, 147.93, 150.75, 193.96, 194.53. MS *m*/*z* (%): 294 (27), 279 (28), 174 (100). HR-FAB$^+$-MS *m*/*z* calcd. for $C_{18}H_{18}N_2O_2$: 294.1368; found: 294.1362.

2-Ethyl-3-methyl-4-(2-formyl)anilino-1,2,3,4-tetrahydroquinoline-8-carboxaldehydes (26c-e) and 2-methyl-3-(2-formyl)anilinopentanal (27)

A reaction effected in the usual manner was complete in 2 days. The mixture from a 2 mmol reaction was absorbed onto silica gel (2 g) and purified by column (4 × 21.5 cm) chromatography on silica gel (143 g) using hexane – ethyl acetate (85:15, 50 mL fractions). F 5–7 contained **26c-e** (135 mg); F 8,9 contained a 1:1 mixture of **26c-e** and **27**; and F 10–12 contained pure **27** (50 mg), all as oils. See Table 3 for the ^{1}H NMR spectra of **26c-e**. The aldehyde **27** was a single isomer. ^{1}H NMR (CD_2Cl_2) δ: 0.96 (t, 3H, *J* = 7.4 Hz), 1.19 (d, 3H, *J* = 7.2 Hz), 1.65 (m, 2H), 2.68 (m, 1H, *J* = 1.2, 4.6, 7.2 Hz), 3.96 (m, 1H), 6.69 (td, 1H, *J* = 0.9, 7.4 Hz), 6.79 (d, 1H, *J* = 8.6 Hz), 7.39 (td, 1H, *J* = 1.7, 7.9 Hz), 7.47 (dd, 1H, *J* = 1.7, 7.7 Hz), 8.41 (bd, 1H, *J* = 9.7 Hz, exchanged with D_2O), 9.69 (d, 1H, *J* = 1.2 Hz), 9.79 (d, 1H, *J* = 0.7 Hz). ^{13}C NMR (CD_2Cl_2) δ: 9.07, 11.05, 26.55, 50.01, 53.94, 111.51, 115.47, 119.01, 136.19, 137.30, 150.90, 194.46, 203.92. MS *m*/*z* (%): 219 (87), 190 (20), 161 (44), 162 (100), 144 (100), 132 (31), 122 (45), 118 (47), 93 (42). HR-FAB$^+$-MS *m*/*z* calcd. for $[C_{13}H_{17}NO_2]H^+$: 220.1337; found: 220.1341.

A reaction effected at 110 °C had a very different product spectrum. Thus, a 2 mmol reaction was carried out in toluene (40 mL) in a pressure bottle for 6 h. Workup as described above gave a mixture, which by TLC (hexane – ethyl acetate (85:15)) showed four major products with *Rf*s 0.88, 0.78, 0.72, and 0.67. The most polar material corresponded to **26c**. The mixture was absorbed onto silica gel (1.5 g) and subjected to column (3.5 × 12 cm) chromatography on silica gel (60 g) using hexane – ethyl acetate (85:15, 25 mL fractions). F 8–10 (112 mg) partially crystallized, and after slurrying with 95:5 hexane – ethyl acetate, crystalline **25b** (8.8 mg, 1.4%), mp 144 to 145 °C, was collected by filtration. F 11–13 (102 mg) contained impure **26c**. F 14,15 (11 mg) was pure **26c**. ^{1}H NMR: see Table 3. ^{13}C NMR (CD_2Cl_2) δ: 6.63, 10.96, 26.46, 54.21, 111.84, 115.36, 116.17, 117.53, 119.66, 122.58, 133.08, 135.78, 136.80, 135.78, 136.80, 137.70, 148.26, 151.17, 194.17, 194.94. MS *m*/*z* (%): 322 (32), 307 (13), 293 (34), 202 (100), 186 (55), 172 (29), 149 (47). HR-EI-MS *m*/*z* calcd. for $C_{20}H_{22}N_2O_2$: 322.1681; found: 322.1667.

trans,*trans*-2-Benzyl-3-phenyl-4-(2-formyl)anilino-1,2,3,4-tetrahydroquinoline-8-carboxaldehyde (26f)

Reaction was carried out in the usual manner, except that the ratio of phenylacetaldehyde to **18a** was 2 and the reaction time was 41 h. Removal of the toluene from a 2 mmol reaction gave a residue, which partially crystallized. The mixture was slurried with toluene; the insoluble solid was collected by filtration and dried to give **26f** (130.5 mg, 14.6%), mp 235–238 °C. A sample was dissolved in hot 1,2-dichloroethane, diluted with four volumes of hexane, and seeded to give material with mp 236–238 °C, after drying in vacuo (75 °C, 6 h). IR (KBr) (cm^{-1}): 3428, 3292, 2751, 2733, 1652. ^{1}H NMR: see Table 3. ^{13}C NMR (CD_2Cl_2) δ: 40.64, 49.56, 55.97, 58.06, 111.71, 115.04, 115.66, 118.07, 118.67, 124.25, 127.25, 127.67, 128.57, 128.79, 129.05, 129.17, 129.38, 129.88, 133.01, 135.77, 136.95, 137.86, 140.14, 146.85, 151.11, 193.68, 194.14. Anal. calcd. for $C_{30}H_{26}N_2O_2$: C 80.69, H 5.87, N 6.27; found: C 80.71, H 5.81, N 6.41.

1,2-Dihydro-2-benzyl-3-phenylquinoline-8-carboxaldehyde (29)

The reaction was carried out as described for the synthesis of **25a** except that the reaction time was 6 h, and the 3-phenylquinoline was removed by extraction with 1 mol L^{-1} HCl. The toluene phase containing **29** was then washed suc-

cessively with 10 wt % sodium carbonate and saturated NaCl solution and then worked up as usual. The crude product from a 2 mmol reaction was absorbed onto silica gel (2 g) and purified by column (4 × 17 cm) chromatography on silica gel (110 g) using hexane – 1,2-dichloroethane (35:65, 25 mL fractions). F 9–13 contained the product (52–115 mg, 13%–29% yield based on phenylacetaldehyde), which was crystalline. After two crystallizations from cyclohexane and drying in vacuo (7 h), it had mp 119.5–121.5 °C. IR (CCl_4) (cm^{-1}): 3313, 2737, 1663. UV (nm): 420.5 (ε 9330), 346.5 (ε 3940), 269 (ε 23 800), 234 (ε 18 600). ^{1}H NMR: see Discussion. ^{13}C NMR (CD_2Cl_2) δ: 43.28, 55.99, 115.99, 118.25, 122.20, 122.67, 125.75, 126.88, 128.36, 128.65, 130.08, 132.61, 135.22, 135.28, 137.66, 138.40, 146.29, 193.44. Anal. calcd. for $C_{23}H_{19}NO$: C 84.89, H 5.89, N 4.30; found: C 84.66, H 5.75, N 4.49.

2-Benzyl-3-phenylquinoline-8-carboxaldehyde (30)

A solution of potassium nitrosodisulfonate (Fremy's salt, 90 mg, 0.335 mmol) in 4 wt % aqueous sodium carbonate (6 mL) was added to a stirred solution of **29** (87 mg, 0.267 mmol) in acetonitrile (9 mL). This caused precipitation of some **29**, but after 1 h a clear solution was obtained. After 6 h, the solution was diluted with a large volume of water and extracted with ethyl acetate. The extract was washed with saturated NaCl solution and then worked up as usual. The crude product was absorbed onto silica gel (0.5 g) and subjected to column (2.2 × 15 cm) chromatographic purification on silica gel (27.5 g) using hexane – 1,2-dichloroethane (35:65, 15 mL fractions). F 4,5 contained the starting material (19 mg), and F 7–21 contained the product (46.5 mg, 66% yield based on starting material consumed). On crystallization from cyclohexane **29** was obtained in two crops, mp 131–132.5 °C (37.5 mg) and mp 126.5–129.5 °C (3.5 mg). Recrystallization of the first crop from cyclohexane gave pure **29**, which had mp 132–132.5 °C after drying in vacuo (6 h). IR (CCl_4) (cm^{-1}): 1692. ^{1}H NMR (CD_2Cl_2) δ: 4.35 (s, 3H), 7.04–7.07 (m, 2H), 7.12–7.20 (m, 3H), 7.31–7.34 (m, 2H), 7.43–7.48 (m, 3H), 7.65 (td, 1H, *J* = 0.7, 7.4 Hz), 8.06 (s, 1H), 8.09 (dd, 1H, *J* = 1.5, 8.1 Hz), 8.26 (dd, 1H, *J* = 1.5, 7.2 Hz), 11.46 (d, 1H, *J* = 0.7 Hz). ^{13}C NMR (CD_2Cl_2) δ: 43.15, 126.32, 126.48, 127.44, 128.28, 128.49, 128.82, 128.88, 129.58, 129.88, 131.69, 134.27, 136.94, 137.19, 139.51, 139.63, 146.84, 160.91, 193.11. Anal. calcd. for $C_{23}H_{17}NO$: C 85.42, H 5.30, N 4.33; found: C 85.62, H 5.28, N 4.50.

Synthesis of quinolines 21 and 37 from 2-aminobenzaldehyde (18a) and methyl alkyl ketones

Neat ketones

A solution of **18a** (121 mg, 1 mmol) in the neat ketone (10 mL) containing ytterbium triflate (62 mg, 0.1 mmol) was placed in an oil bath at 95 °C and stirred in an argon atmosphere for the time given in Table 2, and then the excess ketone was removed in vacuo. Toluene (20 mL) was added to the residue, and the mixture was stirred at reflux temperature in an argon atmosphere for 7 h. After the usual treatment with 10 wt % sodium carbonate solution, the toluene phase was extracted with 1 mol L^{-1} HCl; the extract was made basic with solid sodium carbonate, and the products were extracted into ethyl acetate. The extract was washed with saturated NaCl solution and then worked up as usual.

2,3-Dimethylquinoline (21b) and 2-ethylquinoline (37a)

The crude product was absorbed onto silica gel (1 g) and purified by column (3.5 × 10.5 cm) chromatography on silica gel (49 g) using hexane – ethyl acetate (80:20, 20 mL fractions). F 7–9 contained **37a** (54 mg, 28.2%, converted into the picrate, mp 147–149 °C, lit.(48) value mp 148 °C); F 11–19 contained crystalline **21b** (54 mg, 47.7%), mp 67–78 °C.

2-Methyl-3-ethylquinoline (21c) and 2-n-propylquinoline (37b)

Purified in exactly the same manner as described for **21b** and **37a**. F 2–5 contained **37b** (70 mg, 40.9%, identified by NMR), and F 8–12 contained **21c** (59 mg, 34.5%, mp 69.5–71.5 °C, lit.(49) value mp 74–74.5 °C).

2-Methyl-3-isopropylquinoline (21d) and 2-isobutylquinoline (37c)

Purified as described above. F 3–5 contained **37c** (112 mg, 60.5%, picrate mp 163–166 °C, lit.(50) value mp 163 to 164 °C), and F 8–12 contained **21d** (8 mg, 4.3%). See below for characterization.

From ketones under alkaline conditions

2-Methyl-3-ethylquinoline (21c) and 2-n-propylquinoline (37b)

A solution of **18a** (61 mg, 0.5 mmol) and 2-pentanone (71 mg, 0.82 mmol) in ethanol (3 mL) and 1 mol L^{-1} NaOH (1.75 mL) was left at room temperature for 24 h, diluted with water, and made acidic with 1 mol L^{-1} HCl. The acid solution was extracted with toluene, and then the acid phase was made basic with solid sodium carbonate. The products were extracted with toluene; the extract was washed with saturated NaCl solution and worked up as usual to give the mixture of bases (73 mg, 85.2%), which by ^{1}H NMR was shown to be a 77:23 mixture of **21c** and **37b**.

2-Methyl-3-isopropylquinoline (21d) and 2-isobutylquinoline (37c)

A solution of **18a** (121 mg, 1 mmol) and 4-methyl-2-pentanone (150 mg, 1.5 mmol) in ethanol (6 mL) and 1 mol L^{-1} NaOH (3.5 mL) was heated at reflux temperature under argon for 4 h. The reaction was worked up exactly as described above to give **37c** (144 mg, 77.7%) and **21d** (10 mg, 5.4%). Compound **21d** was an oil. ^{1}H NMR δ: 1.34 (d, 6H, *J* = 6.8 Hz), 2.78 (s, 3H), 3.26 (sept., 1H, *J* = 6.8 Hz), 7.45 (td, 1H, *J* = 1.1, 8.0 Hz), 7.61 (td, 1H, *J* = 1.5, 7.7 Hz), 7.74 (dd, 1H, *J* = 1.2, 81. Hz), 7.92 (s, 1H), 7.99 (d, 1H, *J* = 8.4 Hz). ^{13}C NMR δ: 23.52, 23.54, 29.75, 125.98, 127.49, 127.92, 128.63, 128.86, 131.56, 140.93, 146.51, 158.44. The base was converted into the picrate, mp 216–218 °C decomposition (dec), in hot ethanol. The mp was unchanged on recrystallization and drying in vacuo (60 °C, 14.5 h). Anal. calcd. for $C_{19}H_{18}N_4O_7$: C 55.07, H 4.38, N 13.52; found: C 55.12, H 4.43, N 13.49.

From pyrrolidine enamines 38

A solution of **18a** (121 mg, 1 mmol) and **38a** (51) or **38b** ((52), 2.4 mmol) in anhydrous toluene (10 mL) containing

ytterbium triflate (62 mg, 0.1 mmol) was either left at room temperature or heated at reflux temperature (see Table 2) in an argon atmosphere. HCl (1 mol L^{-1}, 10 mL) was added to the reaction mixture, which was stirred vigorously at room temperature for 15 min. The acidic aqueous phase was worked up as described above to give the crude mixture of bases. This mixture was spiked with hexamethylbenzene (internal standard) and analyzed by ^{1}H NMR.

By arylhydroamination of 1-heptyne

A solution of **18a** (121 mg, 1 mmol), mercuric chloride (472 mg, 1 mmol), and 1-hepytne (0.7 mL, 513 mg, 5.33 mmol) in anhydrous THF (15 mL) was stirred at room temperature for 18 h in an argon atmosphere. Ytterbium triflate (62 mg, 0.1 mmol) was added, and stirring was continued for a total time of 3 days. Even though **18a** was still present by TLC, the solvent was removed in vacuo, water and ethyl acetate were added, and the mixture was filtered through Celite. The organic phase was separated and extracted with 1 mol L^{-1} HCl. The acidic extract was worked up as in the section From pyrrolidine enamines 38 above; the crude mixture was spiked with hexamethylbenzene and analyzed by ^{1}H NMR.

Note added in proof

The Friedländer synthesis of quinolines from *o*-aminoarylketones and ketones also proceeds by a rate-determining aldol mechanism. This is strongly supported by the observation that heating a toluene solution (reflux, 17 h) of 2-hexanone (4 equiv.), *o*-aminoacetophenone (1 equiv.), and pyrrolidine (2 equiv.), containing suspended anhydrous magnesium sulfate (10 equiv., in situ generation of the pyrrolidine enamine of 2-hexanone (53)), and ytterbium triflate (0.1 equiv.), gave a 5.5:1 mixture (ca. 25% yield) of 2-*n*-butyl-4-methylquinoline (kinetic) and 2,4-dimethyl-3-*n*-propylquinoline (thermodynamic). In contrast, effecting the condensation of 2-hexanone and *o*-aminoacetophenone in acetic acid (reflux), containing catalytic sulfuric acid (29), gave a 1:1.7 kinetic to thermodynamic product ratio. Comparable results were obtained starting with 2-butanone and *o*-aminoacetophenone.[2]

References

1. P. Friedländer. Ber. **15**, 2572 (1882).
2. P. Friedländer and C.F. Gohring. Ber. **16**, 1833 (1883).
3. E. Reimann. *In* Houben-weyl. Methoden der organischen chemie. Hetarene II. Part 1. Vol. E7a. G. Thieme Verlag, Stuttgart. 1991. pp. 323–337.
4. C-C. Cheung and S-J. Yan. Org. React. **28**, 37 (1982).
5. G. Jones. *In* The chemistry of heterocylic compounds. Vol. 32. Quinolines. Part 1. *Edited by* G. Jones. John Wiley & Sons, New York. 1977. pp. 181–191.
6. V. Snieckus. Chem. Rev. **90**, 879 (1990).
7. T.G. Majewicz and P. Caluwe. J. Org. Chem. **40**, 3407 (1975).
8. K. Schofield and R.S. Theobald. J. Chem. Soc. 395 (1950).
9. E.A. Fehnel, J.A. Deyrup, and M.B. Davidson. J. Org. Chem. **23**, 1996 (1958).
10. Y. Tamura, T. Tsugoshi, S. Mohri, and Y. Kita. J. Org. Chem. **50**, 1542 (1985).
11. I-S. Cho, L. Gong, and J.M. Muchowski. J. Org. Chem. **56**, 7288 (1991).
12. J.I. Úbeda, M. Villacampa, and C. Avendaño. Synthesis, 1176 (1998).
13. O.B. Familoni, P.T. Kaye, and P.H. Klaas. Chem. Commun. 2563 (1998).
14. Y. Hsiao, N.R. Rivera, N. Yasuda, D.L. Hughes, and P.J. Reider. Org. Lett. **3**, 1101 (2001).
15. V.B. Drewsen. Ber. **16**, 1953 (1883).
16. A. Baeyer and V. Drewsen. Ber. **15**, 2854 (1882).
17. S-D. Cho, W-Y. Choi, S-G. Lee, Y-J. Yoon, and S.C. Shin. Tetrahedron Lett. **37**, 7059 (1996).
18. K. Ramadas and N. Srinivasan. Synth. Commun. **22**, 3189 (1992).
19. I.L. Smith and J.W. Opie. Org. Synth. Coll. Vol. 3, 56 (1955).
20. B.D. Foy, R.A. Smudde, and W.F. Wood. J. Chem. Educ. **7**0 322 (1993).
21. G.P. Black, F. Dimon, S. Fratucello, P.J. Murphy, M. Nielson, and H.L. Williams. Tetrahedron, **52**, 8001 (1996).
22. A.T. Nielsen and W.J. Houlihan. Org. Syn. **16**, 1 (1968).
23. M.B. Smith and J. March. *In* March's advanced organic chemistry. Reactions, mechanisms, structure. 5th ed. John Wiley & Sons, Inc. New York. 2002. pp. 285–286.
24. H.O. House and R.S. Ro. J. Am. Chem. Soc. **80**, 2428 (1958).
25. D.S. Noyce and M.J. Jorgensen. J. Am. Chem. Soc. **83**, 2525 (1961).
26. J.E. Dubois and M. Dubois. Compt. Rend. **256**, 715 (1963).
27. T. Vondrák and M. Procházka. Coll. Czech. Chem. Commun. **48**, 82 (1983).
28. D.M. Sammond and T. Sammakia. Tetrahedron Lett. **37**, 6065 (1996).
29. E.A. Fehnel. J. Org. Chem. **31**, 2899 (1966).
30. G. Barbieri, P. Lazzaretti, L. Schenetti and F. Taddei. Org. Magn. Res. **7**, 451 (1975).
31. M. Funabashi, M. Iwakawa, and J. Yoshimura. Bull. Chem. Soc. Jpn. **42**, 2885 (1969).
32. S. Talukdar, C-T. Chen, and J-M. Fang. J. Org. Chem. **65**, 3148 (2000).
33. P.A. Wehrli and B. Schaer. Synthesis, 288 (1974).
34. J.B. Wommack, T.G. Barbee, D.J. Thoennes, M.A. McDonald, and D.E. Pearson. J. Heterocycl. Chem. **6**, 243 (1969).
35. E.M. Hawes and D.K.J. Gorecki. J. Heterocycl. Chem. **11**, 151 (1974).
36. G. Kempter, P. Andratschke, D. Heilmann, H. Krausmann, and M. Mietasch. Chem. Ber. **97**, 16 (1964).
37. P.G. Dormer, K.K. Eng, R.N. Farr, G.R. Humphrey, J.C. McWilliams, P.J. Reider, J.W. Sager, and R.P. Volante. J. Org. Chem. **68**, 467 (2003).
38. P. Dalla Croce, P. Ferruti, and R. Stradi. Gazz. Chim. Ital. **97**, 589 (1967).
39. D. Pocar, G. Bianchetti, and P. Ferruti. Gazz. Chim. Ital. **97**, 597 (1967).
40. G.W. Fischer. J. Prakt. Chem. **330**, 981 (1988).
41. J. Barluenga, F. Aznar, R. Liz, and R. Rodes. J. Chem. Soc. Perkin Trans. 1, 2732 (1980).
42. A. Capperucci, A. Degl'Innocenti, M. Funicello, G. Mauriello, P. Scafato, and P. Spagnolo. J. Org. Chem. **60**, 2254 (1995).
43. H. Horina and N. Inoue. J. Org. Chem. **46**, 4416 (1981).
44. A. Rilliet. Helv. Chim. Acta, **5**, 547 (1922).

[2] J.M. Muchowski. Unpublished results.

45. J. Buckingham (*Editor*). Dictionary of organic compounds. Vol. 4. 5th ed. Chapman & Hall, London. 1982. p. 4053.
46. J.H. Markgraf, R.J. Katt, W.L. Scott, and R.N. Sherfin. J. Org. Chem. **34**, 4131 (1969).
47. M.P. Maguire, K.R. Sheets, K. McVety, A.P. Spada, and A. Ziberstein. J. Med. Chem. **37**, 2129 (1994).
48. R. Delaby and J. Hiron. Bull. Soc. Chim. Fr. **47**, 1395 (1930).
49. N. Satoshi. Yakugaku Zasshi. **81**, 479 (1961); Chem. Abstr. **55**, 105 853 (1961).
50. T. Higashino, K. Suzuki, and E. Hayashi. Chem. Pharm. Bull. **23**, 746 (1975).
51. R. Jacquier, C. Petrus, and F. Petrus. Bull. Soc. Chim. Fr. 2845 (1966).
52. J. Koyama, I. Toyokuni, and K. Tagahara. Chem. Pharm. Bull. **46**, 332 (1998).
53. P.A. Zoretic, F. Barcelos, and B. Branchaud. Org. Prep. Proced. Int. **8**, 211 (1976).