# Mechanism of the Skraup and Doebner–von Miller Quinoline Syntheses: Cyclization of α,β-Unsaturated *N*-Arylimininium Salts via 1,3-Diazetidinium Ion Intermediates[1]

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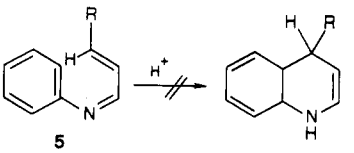
The hydrochlorides of cinnamaldehyde anils of the type ArCH=CHCH=NAr′, where Ar and Ar′ are phenyl or *p*-tolyl groups, have been shown to react between 25 °C and 100 °C, in a toluene suspension or in a solution of DMSO or acetonitrile, to yield 2-substituted quinolines and *N*-cinnamylanilines ArCH=CHCH$_2$NHAr′. The reaction proceeds under anhydrous conditions by cyclization of the anil hydrochlorides themselves to produce ultimately 2-substituted quinolines. The kinetics of the reaction follow a first-order dependence on the anil hydrochloride. Rapid exchange occurring between dissimilar anil hydrochlorides suggests that such anil metatheses take place by way of 1,3-diazetidinium ion intermediates, which previous studies have shown would possess the requisite metastability. The foregoing experimental observations are reconciled in terms of a novel mechanism for the formation of quinolines directly from anils under acidic conditions, namely, the reversible formation of diazetidinium ions and their irreversible cyclization to quinolines. It is proposed that this pathway is the operative mechanism in the classic Skraup and Doebner–von Miller quinoline syntheses.

Over a century ago, Skraup discovered that quinoline could be synthesized by heating aniline with glycerine, sulfuric acid, and an oxidizing agent.[3] By substituting 1,2-glycols or an α,β-unsaturated aldehyde for the glycerine, Doebner and von Miller were able to generalize Skraup's method for the synthesis of quinolines bearing substituents in the pyridinoid ring.[4] These quinoline syntheses have proved of great value and scope for constructing this important heterocyclic system.[5] Despite the numerous instances of successful quinoline syntheses, however, relatively little has been established concerning the detailed mechanism of these reactions.

It is generally agreed that glycerine is dehydrated to form acrolein in the Skraup reaction and that ethylene glycol is dehydrated to acetaldehyde, which is in turn condensed to crotonaldehyde, in the Doebner–von Miller procedure. Then, in a series of steps open to controversy the aniline (**1**) and α,β-unsaturated aldehyde **2** combine to yield a 2-substituted 1,2-dihydroquinoline (**3**) (Scheme I). In the Skraup procedure, an added oxidant, such as nitrobenzene, aromatizes the dihydro intermediate to the final quinoline **4**; in the Doebner–von Miller procedure, hydrogen is transferred from **3** to Schiff bases present in the mixture (e.g., $CH_3CH{=}NC_6H_5$) with the formation of secondary amines ($CH_3CH_2NHC_6H_5$).[6]

What the nature is of the intermediate steps between **2** and **3** continues to be uncertain. Skraup himself made the straightforward suggestion that the Schiff base **5** formed between **1** and **2** undergoes acid-catalyzed cyclization.[7] But this interpretation was considered to be untenable by the finding that α,β-unsaturated aldehydes **2** gave exclusively 2-substituted 1,2-dihydroquinolines **3** (Scheme I); direct cyclization of **5** should have led to 4-substituted 1,4-dihydroquinolines **6** (eq 1). To accommodate this actual course of reaction, Bischler proposed that the aldehyde **2** or its Schiff base **5** underwent a 1,4-addition of the aniline to give the β-anilino aldehyde **7** or

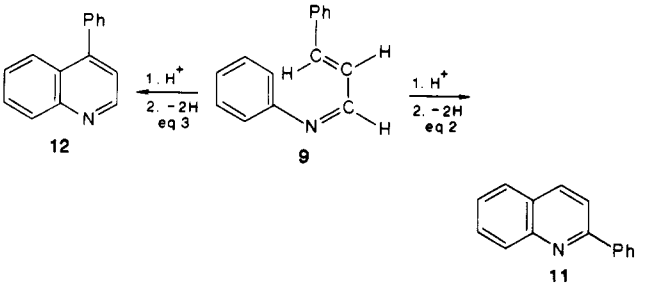



5 6 (1)

imine **8** and this adduct underwent elimination of water (with **7**) or of aniline (with **8**) to lead to the formation of the final dihydroquinoline **3** (Scheme I).[8] Subsequent studies employing milder, hydrolyzing conditions have detected uncyclized and cyclized derivatives of **3**, **7** or **8**, which have been interpreted as cogent evidence in favor of Bischler's mechanism.[9-12]

Nevertheless, considerable doubt remains whether Skraup's original suggestion of the crucial intermediacy of Schiff base **5** is mistaken. It is certainly true that a simple cyclization of **5**, as depicted in eq 1, cannot be invoked. But it is conceivable that **5** might lead to the appropriately substituted quinoline **4** by some less obvious mechanistic pathway.

In the present study we wished to test whether such a preformed anil itself, namely, cinnamaldehyde anil (**9**) or its anhydrous hydrochloride salt (**10**), could be made to cyclize to 2-phenylquinoline (**11**) (eq 2), rather than the expected 4-phenylquinoline (**12**) (eq 3; cf. eq 1), under reaction conditions similar to those employed in these quinoline syntheses.

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(1) Paper 6 of the series Rearrangements of Heterocyclic Compounds. For paper 5, see: Eisch, J. J.; Sanchez, R. *J. Org. Chem.* **1986**, *51*, 1848.
(2) Present address: Laboratory of Technological Processes, Faculty of Chemistry, Warsaw Technical University, Warsaw, Poland.
(3) Skraup, Z. H. *Ber. Dtsch. Chem. Ges.* **1880**, *13*, 2086.
(4) Doebner, O.; von Miller, W. *Ber. Dtsch. Chem. Ges.* **1881**, *14*, 2812.
(5) Manske, R. H. F.; Kulka, M. *Organic Reactions*; Adams, R., Ed., John Wiley & Sons: New York, Vol. 7, 1953; p 59.
(6) Mills, W. H.; Harris, J. E. G.; Lambourne, H. *J. Chem. Soc.* **1921**, *119*, 1294.
(7) Skraup, Z. H. *Ber. Dtsch. Chem. Ges.* **1882**, *15*, 897.
(8) Bischler, A. *Ber. Dtsch. Chem. Ges.* **1892**, *25*, 2864.
(9) Jones, H. O.; Evans, P. E. *J. Chem. Soc.* **1911**, *99*, 334.
(10) Edwards, M. G.; Garrod, R. E.; Jones, H. O. *J. Chem. Soc.* **1912**, *101*, 1376.
(11) von Miller, W.; Plöchl, J. *Ber. Dtsch. Chem. Ges.* **1896**, *29*, 1469.
(12) (a) Badger, G. M.; Crocker, H. P.; Ennis, B. C.; Gayler, J. A.; Matthews, W. E.; Paper, W. C. G.; Samuel, E. C.; Spotswood, J. M. *Aust. J. Chem.* **1963**, *16*, 814. (b) Forrest, T. P.; Dauphinee, G. A.; Miles, W. F. *Can. J. Chem.* **1969**, *47*, 2121.

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**Scheme I**

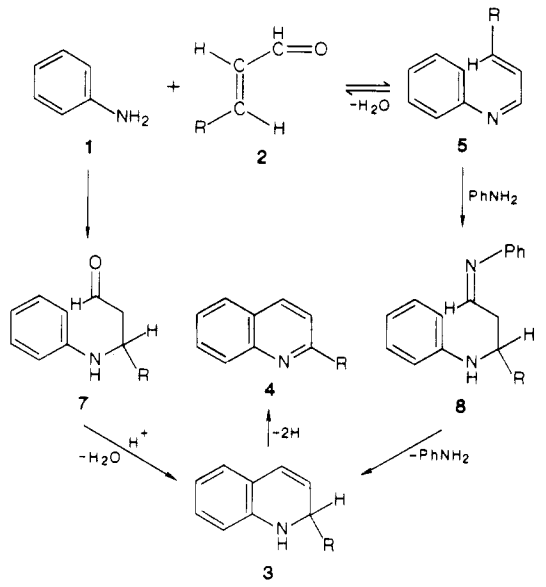


**Table I. Typical Kinetic Data for the Reaction of Cinnamaldehyde Anil Hydrochloride (10) in DMSO and Regression Analysis for First-Order Rate Dependence[a]**

| aliquot | amount of 9[b] (mg) | time (actual) (min) | time (computed)[c] (min) |
|---|---|---|---|
| 1 | 422.8 | 0 | |
| 2 | 387.7 | 14.00 | 12.98 |
| 3 | 346.9 | 30.00 | 28.72 |
| 4 | 306.0 | 45.00 | 46.90 |
| 5 | 166.7 | 133.00 | 134.94 |
| 6 | 109.8 | 197.00 | 195.46 |

[a] A 487-mg sample of **10** (2.0 mmol) was dissolved in 30.0 mL of anhydrous DMSO and maintained at 64.0 ± 0.1 °C. [b] The remaining amount of free anil was determined by alkaline hydrolysis of an aliquot withdrawn and quenched at time $t$. [c] The computed time for first-order dependence was found from inserting the remaining amount of **9** found at time $t$ into the expression $t$(computed) = 876.5–144.9 $\log_e$ [**9**].

In undertaking this test, we had to avoid the presence of water, so as to eliminate the possibility that **9** might hydrolyze under the acidic conditions and thereby be able to generate aldehyde **7** or Schiff base **8** (Scheme I, R = Ph) and thus yield **11** via Bischler's pathway.[13] By working in carefully dried dimethyl sulfoxide, we found that we could study the reactions of cinnamaldehyde anil (**9**) and its derivatives, as their hydrochloride salts, in a homogenous medium over the convenient temperature range of 50–100 °C.

## Results

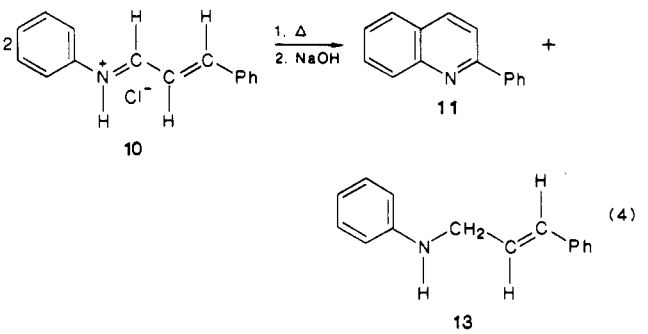
**Thermal and Photolytic Stability of Cinnamaldehyde Anil (9).** The anil **9** proved to be thermally stable up to approximately 200 °C; at temperatures of about 250 °C, however, profound decomposition occurred, leading to the evolution of aniline and the formation of an intractable dark tar. On the other hand, no change was observed in samples of **9** irradiated in benzene or hexane solution at 254 nm for 24 h or longer.[14]

**Table II. Formation of 2-Phenylquinoline (11) from Two Solutions, One Containing Only Cinnamaldehyde Anil Hydrochloride (10) and the Other Containing Both Cinnamaldehyde Anil (9) and 10[a]**

| aliquot | time (s) | 11 from 10 (mg) | 11 from 9 + 10 (mg)[b] |
|---|---|---|---|
| 1 | 0 | | |
| 2 | 14.00 | 3.08 | 3.59 |
| 3 | 30.00 | 8.15 | 11.68 |
| 4 | 45.00 | 14.89 | 18.87 |
| 5 | 133.00 | 44.52 | 53.92 |
| 6 | 197.00 | 57.60 | 66.18 |

[a] Both the solution of **10** and that of **10** + **9** had the same amount of **9** (422.8 mg, 2.0 mmol) dissolved in 30.0 mL of anhydrous DMSO, but in the first solution there was 1 equiv of HCl; in the second solution, only 1/2 equiv. [b] Although not linear, the amount of **11** formed from **9** + **10** at time $t$ is consistently greater than that formed from **10** alone.

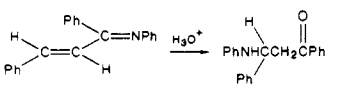
**Thermal Behavior of Cinnamaldehyde Anil Hydrochloride (10).** This hydrochloride underwent smooth decomposition when heated between 50 °C and 100 °C, either in toluene suspension or in solutions of anhydrous acetonitrile or dimethyl sulfoxide (DMSO). Hydrolytic workup under basic conditions yielded 2-phenylquinoline (**11**) and *N*-cinnamylaniline (**13**) as the only products detected (eq 4); the presence of 4-phenylquinoline (**12**), in particular, was ruled out.



All these reactions were conducted under an atmosphere of dry nitrogen, with anhydrous solvents and the rigorous exclusion of moisture.

The rate of disappearance of the anil hydrochloride **10** could be conveniently measured at 64.0 ± 0.1 °C through about 75% conversion (Table I). A regression analysis of the kinetic data in terms of models for first-order, three-halves-order, and second-order dependence on the concentration of **10** showed that the best fit of the data was given by a first-order dependence ($R^2$ = 0.999 and standard error of 2.04). The fits for three-halves order ($R^2$ = 0.997 and standard error of 4.72) and second order ($R^2$ = 0.985 and standard error of 11.15) were less satisfactory.[15]

(13) Eisch, J. J.; Sanchez, R. *J. Org. Chem.* **1986**, *51*, 1848. Illustrative of the ease of the hydrolytic rearrangement of such anils is our finding that chalcone anil readily forms the β-anilino ketone in dilute aqueous acid at 25 °C:



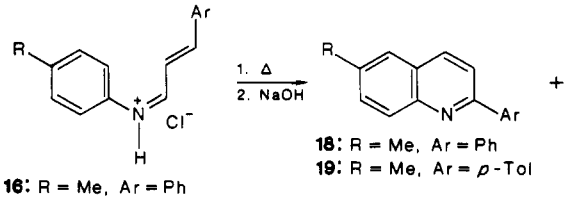
(14) The photoreaction of **9** to produce **11** in low yield has been reported, but the irradiation of **9** was conducted with a high-pressure mercury lamp and in solutions of acetic acid or in a methanolic solution of $FeCl_3 \cdot 6H_2O$. In neither case was moisture excluded, nor can the thermal, rather than photochemical, formation of **9** be ruled out (Ogata, Y.; Takagi, K. *Tetrahedron* **1971**, *27*, 1573). From the work of Ingold and Piggott any 1,3-diazetidine formed under these conditions would not be expected to be stable (cf. ref 23).

(15) The regression analysis of the kinetic data in terms of a fit for first-order, three-halves, or second-order dependence on **10** was carried out with a computer program described in the graphic and statistics program B/GRAPH published by Batteries Included, Toronto, Canada, 1984, and designed for Atari 8-bit computers. The coefficient of determination, $R^2$, is a measure of the closeness of the fit, 1.000 being perfect. The standard error of estimate indicates the relative deviations of the data points about the regression curve, a value of zero being none.

Because at least two principal products, **11** and **13**, were formed in this complex, multistep reaction, kinetic data on the rate of formation of 2-phenylquinoline could not be as readily analyzed. Nevertheless, an instructive comparison of relative rates of forming **11** was made by monitoring two separate reaction solutions: one solution containing 2 molar equiv of the hydrochloride of cinnamaldehyde anil (**10**) and the other solution containing 1 molar equiv each of **9** and **10**. Even though both solutions contained the same concentration of anil **9**, the solution having the anil only as its hydrochloride (i.e., no free anil base) formed 2-phenylquinoline at a rate about 80% that at which the 1:1 mixture of **9** of **10** did (Table II).

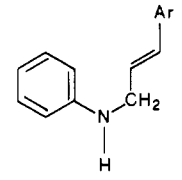
Two samples of **10** in scrupulously dried DMSO were heated simultaneously at 64 °C in order to test the possible influence of water on the rate and course of reaction, but to one of the samples 1.5 molar equiv of water was first added. By monitoring the products formed and the anil remaining in the aliquots withdrawn at intervals, it was ascertained that the same products were formed from both samples and that the sample of **10** containing the water reacted at a somewhat slower rate.

**Thermal Behavior of Methyl-Substituted Cinnamaldehyde Anils (14, 15) and Their Hydrochlorides (16, 17).** For the purpose of ascertaining whether either of the aryl groups in **10** changed their bonding to the C=CC=N framework during cyclization to the quinoline, both the hydrochlorides of *N*-cinnamylidene-*p*-toluidine (**14**) and *N*-(*p*-methylcinnamylidene)-*p*-toluidine (**15**) were individually allowed to rearrange in warm DMSO. In both cases, the expected, analogous quinolines (**18**, **19**) and the substituted *N*-cinnamylanilines (**20**, **21**) were formed (eq 5). Thus, no *cine* substitution on either of the benzene rings is involved during the formation of the quinolines **18** and **19**.[16]




**16**: R = Me, Ar = Ph
**17**: R = Me, Ar = *p*-Tol

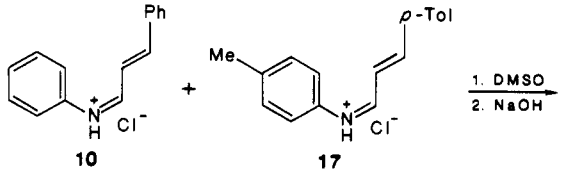
**18**: R = Me, Ar = Ph
**19**: R = Me, Ar = *p*-Tol



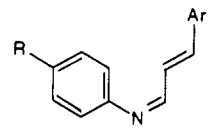

(5)

**20**: R = Me, Ar = Ph
**21**: R = Me, Ar = *p*-Tol

In order to establish whether the quinoline synthesis was intramolecular or intermolecular, we intended to conduct a cross-over reaction by allowing a 1:1 mixture of the hydrochlorides of cinnamaldehyde anil (**9**) and *N*-(*p*-methylcinnamylidene)-*p*-toluidine (**15**) to undergo rearrangement. Were the quinoline synthesis intermolecular, then four different quinolines would be expected, whereas an intramolecular cyclization should yield only two. But before we undertook such a cross-over experiment, we had to ascertain whether such a 1:1 mixture of **10** and **17** in DMSO was stable to exchange at 25 °C. In conducting such a test, we observed an astonishing result: after 5 min of allowing **10** and **17** to stand in DMSO and then hydrolyzing the mixture with aqueous NaOH, a mixture of cinnamaldehyde anil (**9**), *N*-(*p*-methylcinnamylidene)-*p*-toluidine (**15**), and the two monomethyl anils, *N*-cinnamylidene-*p*-toluidine (**14**) and *N*-(*p*-methylcinnamylidene)aniline (**22**), was obtained (eq 6).




**10** **17**




(6)

**9**: R = H, Ar = Ph
**14**: R = Me, Ar = Ph
**15**: R = Me, Ar = *p*-Tol
**22**: R = H, Ar = *p*-Tol

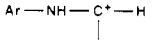
That the exchange of the cinnamylidene and anilino groups occurred between the hydrochlorides **10** and **17**, rather than between the free Schiff bases **9** and **15**, was demonstrated by allowing a 1:1 mixture of **9** and **15** to stand for 48 h at 25 °C in DMSO and then hydrolyzing the mixture with aqueous NaOH. Only **9** and **15** were found in the hydrolyzed mixture.

Not only did such anil hydrochlorides undergo ready group exchange with each other, but they also exchanged the anil moiety with free aromatic amines. Thus, admixing cinnamaldehyde anil hydrochloride (**10**) with 1 molar equiv of *p*-toluidine in DMSO for 5 min at 25 °C and treating the mixture to an alkaline hydrolytic workup provided a mixture of cinnamaldehyde anil (**9**), *N*-cinnamylidene-*p*-toluidine (**14**), aniline, and *p*-toluidine.

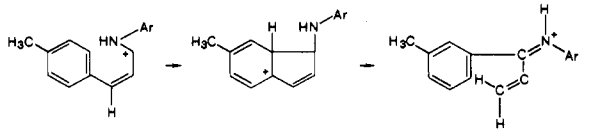
## Discussion

From the preceding observations, we conclude that the hydrochlorides of the cinnamaldehyde anils themselves undergo rearrangement to produce to 2-arylquinolines. For cyclizations under these experimental conditions, the pathway first suggested by Bischler and depicted in Scheme I does not apply, for there are no significant amounts of water present,[17,18] which is required to convert **5** into **7**, nor of aniline, which is required to convert **5** into **8**. In kinetic studies of the rate of consumption of anil hydrochloride **10**, the intentional addition of small amounts of water to the DMSO did not accelerate the reaction but

(16) Were the *p*-tolyl group in the β-position of **17** to be attacked electrophilically by the cation center,




it would become a *m*-tolyl group:



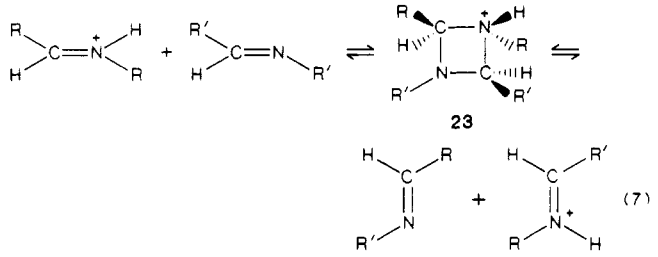

(17) Worries over the possible role of moisture in these or any reaction invokes the specter of H. B. Baker ("Bone-Dry" Baker), who maintained that many reactions, such as even that between nitric oxide and oxygen, do not occur in the complete absence of water. His inevitable question after any scientific lecture was said to be: "Were your reagents really dry?" However, such imputing of extraordinary catalytic action to water has often been discredited by subsequent experiments (Glasstone, S. *Textbook of Physical Chemistry*, 2nd ed.; Van Nostrand: New York, 1946; p 1130. In the present work the anil hydrochlorides were prepared and allowed to react with scrupulous exclusion of atmospheric moisture.

(18) The DMSO used as a reaction solvent was dried by a procedure known to leave less than 0.05% of residual water. Garnsey, R.; Prue, J. E. *Trans. Taraday Soc.* **1968**, *64*, 1206.

rather retarded the rate somewhat.[19]

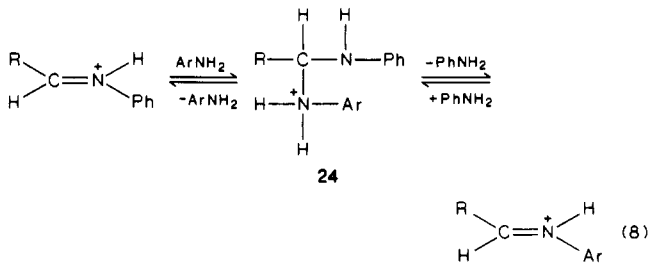
The present study shows further that neither the pyrolysis of anil **9** under 200 °C nor its irradiation at 254 nm[14] causes formation of the quinoline. That either the anil hydrochloride **10** or a 1:1 mixture of **9** and **10** do react to produce 2-phenylquinoline at comparable rates demonstrates that the reaction is acid-catalyzed.

The remarkably facile exchange of anil fragments observed between **10** and **17** in DMSO at 25 °C cannot be explained by a reversible hydrolysis–reformation of the anil (**1** + **2** → **5** in Scheme I) under these anhydrous conditions. An efficient pathway for such an anil metathesis-like reaction would be the reversible formation of a dicationic or monocationic diazetidinium intermediate **23** and its resplitting into the components or into the products. Formation of **23** as a monocation is more attractive from an electrostatic standpoint; such a monocation might result from the transfer of a proton from the anil hydrochloride to DMSO[20] (eq 7).




(7)

Similar to the foregoing exchange mechanism, the ready exchange of anil moieties between cinnamaldehyde anil hydrochloride (**10**) and *p*-toluidine can be explained by the formation of geminal dianilino cation **24** and the reelimination of the aniline (eq 8).

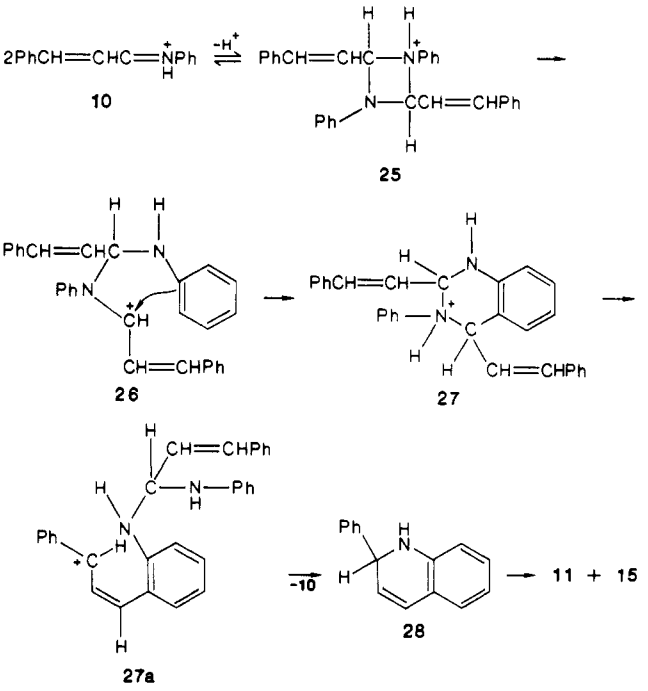



(8)

In addition to the foregoing information on the influence of heat, acid, water, and solvent on the rate of cyclization and exchange reactions of these anils, the kinetics for the disappearance of the anil hydrochloride **10** were measured and found to be first order in **10** (Table I). Furthermore, a 1:1 mixture of **9** and **10**, having the same total concentration of **9** as was present in a solution of pure **10**, underwent reaction at a somewhat faster rate (1.2 times).

In order to integrate all of these experimental observations into a rational mechanism, we propose the reversible formation of labile diazetidinium cation intermediates (**25**), similar to **23**, and the irreversible cyclization through **26**

**Scheme II**




to yield **27**, followed by elimination of 1 mol of **10** and the generation of 2-phenyl-1,2-dihydroquinoline (**28**).[21] In a rapid step, hydride-ion transfer would then occur between **10** and **28** to yield the final products, **11** and **13** (Scheme II).

That the proposed irreversible step, **25** → **28**, regenerates 1 mol of **10** is consistent with the observed first-order kinetic dependence on **10**. Furthermore, the reversible formation of diazetidinium monocation **25** finds support in the comparable rates at which solutions of pure **10** and of 1:1 mixtures of **10** and **9** react to form **11**.

The conceptual basis for this unusual cyclization of **10** to form **11** is the generation of such 1,3-diazetidines by cycloaddition and their instability under acidic conditions.[22] Not only the present work on the ready anil exchange occurring between **10** and **17** (eq 6) speaks for the reversible formation of diazetidinium ions in DMSO (**23** in eq 7) but some 65 years ago Ingold reported the first evidence for such anil metatheses.[23] In a telling example, a mixture of (*m*-nitrobenzylidene)aniline and benzylidene-*p*-bromoaniline was heated in benzene solution at 90 °C for several weeks. Workup yielded both the starting anils as well as the anils expected from exchange, namely, benzylideneaniline and (*m*-nitrobenzylidene)-*p*-bromoaniline. In the absence of acids and polar functional

(19) We also were concerned that contact between the anil hydrochlorides and DMSO might generate water in situ because *free*, gaseous HCl reacts with DMSO in the presence of Linde molecular sieves to produce chlorine and water (Rynbrandt, R. H. *Tetrahedron Lett.* **1971**, 2919). However, were such a reaction to take place between **10** and DMSO, then chlorination of **9** or **10** should have occurred (Zalukaev, L. *Zh. Obshch. Khim.* **1952**, *212*, 491; *Chem. Abstr.* **1953**, *47*, 2132). But no such chlorinated anils, quinolines or cinnamylanilines were observed in the present study.

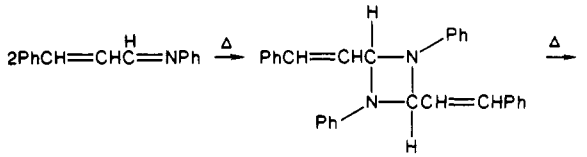
(20) Dimethyl sulfoxide is a base of comparable strength to water and thus might compete with the free anil for a proton (Kolthoff, I. M.; Reddy, T. B. *Inorg. Chem.* **1962**, *1*, 189). Anils are relatively weak bases. In addition, DMSO has a high dielectric constant (46.7 at 25 °C) and is an excellent solvent for salts.

(21) In our literature search on 1.3-diazetidines we came upon the remarkable report of an apparently acid-stable 1,3-diazetidine resulting from the photodimerization of *N*-benzylidene-cyclohexylamine (Kan, R. O.; Furey, R. L. *J. Am. Chem. Soc.* **1968**, *90*, 1666). We repeated the photosynthesis of this supposed 1,3-diazetidine and subjected it to hydrogenolysis with dihydrogen in the presence of palladium-on-charcoal. No toluene but only bibenzyl was formed by such cleavage. Hence, the photodimer is not a 1,3-diazetidine (Cf. Padwa, A.; Bergmark, W.; Pashayan, D. *J. Am. Chem. Soc.* **1969**, *91*, 2653).

(22) Intermediate **27** would be expected to isomerize readily into **27a**, because the transformation involves the cleavage of a nitrogen–carbon bond, whose carbon is both allylic and benzylic in character and hence is able to stabilize the carbenium ion developing in the transition state of such a N–C bond rupture.

(23) In the course of conducting anil metatheses, as exemplified by eq 7, intermediates were isolated that were considered to be 1,3-diazetidines. Fusing such adducts or heating them in alcohols caused the anil metathesis products to form (Ingold, C. K.; Piggott, H. A. **1922**, *121*, 2793). Whether these intermediates are in fact 1,3-diazetidines, rather than 1:1 hydrogen-bonded or charge-transfer complexes, remains to be established.

groups, it is also clear from the work of Ingold and our studies that such diazetidines are formed only with difficulty below 50 °C. Indeed, the thermal instability of **9** over 200 °C, where aniline is smoothly evolved, may best be explained by the formation of diazetidine **29** and the elimination of aniline (eq 9).



**29**

$$PhNH_2 + (PhCH{=}C{=}CH)_2NPh \quad (9)$$

In conclusion, therefore, we have shown that the protonated cinnamaldehyde anils themselves undergo cyclization to give the corresponding 2-substituted quinoline under conditions where formation of the β-anilinopropionaldehyde (**7**) or the related anil (**8**) is not involved (Scheme I). Since the most readily formed derivative in both the Skraup and the Doebner–von Miller reactions is the Schiff base **5**, we judge that Skraup was correct in assuming that **5** is the critical intermediate in these quinoline syntheses. Our observation of the rapid exchange between anil hydrochlorides (eq 6) points to the intermediacy of diazetidinium ions, which we conclude undergo irreversible cyclization to yield the 2-substituted 1,2-dihydroquinoline (Scheme II). In mixtures of acetic and sulfuric acids at 50 °C[12a] or a solution of ethanol and water,[12b] intermediates of type **7** or cyclized isomers of **8** can be isolated, and at higher temperatures these intermediates do then yield the expected quinoline. But such reaction conditions foster the prior hydrolysis of any anil and its transformation to the β-anilinopropionaldehyde. Under the usual conditions of the Skraup or Doebner–von Miller reactions, direct heating of the components would first form the anil under acidic conditions that have now been shown to cause direct cyclization of the anil itself. In summary, then, we would invoke Occam's razor and conclude that it is more likely that all such quinoline syntheses proceed principally by way of the direct cyclization as anils as depicted in Scheme II. Cyclization of the β-anilinopropionaldehyde is probably only a minor pathway.

## Experimental Section

**General Techniques.** All reactions involving the anils or their hydrochlorides were conducted under an atmosphere of dry, oxygen-free nitrogen gas, which was purified according to published procedures.[24] Reaction solvents, such as benzene, toluene, and acetonitrile, were freed of protic impurities by known methods and given a final distillation from the appropriate drying agent in an atmosphere of dry nitrogen. Subsequent transfers of such anhydrous solvents were made with nitrogen-flushed, gas-tight syringes.

The dimethyl sulfoxide (DMSO) used in these experiments was purified and dried in the following manner:[13] Commercially available dimethyl sulfoxide (99+%; <0.05%) was stored over 3A Linde molecular sieves for several days and stirred over powdered calcium hydride at 50 °C for 24 h. Finally, the DMSO was fractionally distilled from calcium hydride under a nitrogen atmosphere at reduced pressure from a carefully dried distillation apparatus. Such DMSO so purified has been reported to contain 0.002% of water or less.

All reaction vessels were dried in an oven at 140 °C for at least 4 h and then assembled with a T-connection to the nitrogen source and to high vacuum. Such hot vessels were alternately evacuated and refilled with nitrogen while being cooled to 25 °C.

The melting points were measured in a Thomas-Hoover capillary melting point apparatus and are uncorrected. Chromatographic separations were effected either with a Perkin-Elmer Model 400 liquid chromatograph or with a Hewlett-Packard Model 5880A gas chromatograph. Spectral data were obtained with the following instruments: $^1H$ NMR, Varian EM-360; IR, Perkin-Elmer Model 457 or 238B; UV, Cary Model 14; and MS, Hewlett-Packard Model 5993.

**Starting Materials.** *trans*-Cinnamaldehyde, aniline, *p*-toluidine, cyclohexylamine, and benzaldehyde were commercially available and were either distilled under nitrogen or recrystallized before use. *p*-Methylcinnamaldehyde was synthesized by a published procedure,[25] as was *N*-benzylidenecyclohexylamine.[26]

The Schiff bases of the cinnamaldehydes and aromatic amines were all prepared in a procedure analogous to the following specific procedure for cinnamaldehyde anil (**9**). Thus, a mixture of 13.2 g (0.10 mol) of *trans*-cinnamaldehyde and 10.2 g (0.11 mol) of aniline in 40 mL of methylene chloride was treated with 100 mg of *p*-toluenesulfonic acid and then allowed to stand at 20–25 °C. When the mixture became turbid due to the formation of water, 25 g of 3A Linde molecular sieves was added and the mixture then agitated for 45 min. The mixture was filtered, the filtrate evaporated under reduced pressure, and the residue recrystallized from 95% ethanol. In this manner, 17.6 g (85%) of cinnamaldehyde anil was obtained, pale yellow solid, mp 105–106 °C.

In a similar manner, *N*-cinnamylidene-*p*-toluidine (**14**), mp 80–81.5 °C, and *N*-(*p*-methylcinnamylidene)-*p*-toluidine (**15**), mp 142–142.7 °C, were prepared as yellow solids.

Compound **14**: $^1H$ NMR ($CDCl_3$) 2.42 (s, 3 H), 7.2–7.8 (m, 10 H), and 8.4 (t, H). Anal. Calcd for $C_{16}H_{15}N$: C, 83.83; H, 6.83. Found: C, 83.71; H, 6.67.

Compound **15**: $^1H$ NMR ($CDCl_3$) 2.37 (s, 6 H), 7.1–7.6 (m, 10 H), and 8.36 (t, H). Anal. Calcd for $C_{17}H_{17}N$: C, 86.81; H, 7.23. Found: C, 86.66; H, 7.31.

**Hydrochlorides of the Schiff Bases (9, 14, and 15).** These hydrochlorides were prepared in accordance with the following procedure for cinnamaldehyde anil. Thus, a solution of 20.9 g (0.10 mol) of **9** in 50 mL of dry toluene was treated with a stream of hydrogen chloride gas, which was generated by dropping concentrated $H_2SO_4$ onto powdered NaCl, and was then passed through a tube filled with a mixture of $P_2O_5$ on glass beads. The precipitated hydrochloride **10** was filtered off, resuspended in fresh toluene, and filtered again. Resuspension of **10** and filtration were repeated once more from toluene and twice from hexane. The bright yellow hydrochloride was then dried under vacuum at 25 °C; when pure and kept under an inert atmosphere, **10** can be stored for extended periods at 25 °C. It does not melt but undergoes decomposition when heated up to 110 °C; $^1H$ NMR (DMSO-$d_6$) 7.4–8.0 (m, 12 H), 9.4 (d, 0.5 H, $J$ = 8 Hz), and 9.7 (d, 0.5 H, $J$ = 8 Hz).

In an analogous manner, hydrochlorides of **14** and **15** can be made.

Compound **16**: $^1H$ NMR ($CDCl_3$) 2.41 (two s of unequal height (1.6:1.0), 3 H), 7.4–8.0 (m, 12 H), 9.4 (d, 0.7 H, $J$ = 8 Hz), and 9.8 (d, 0.3 H, $J$ = 8 Hz).

Compound **17**: $^1H$ NMR ($CDCl_3$) 2.40 (unresolved doublet of equal intensity), and 7.4–8.0 (m).

**Thermal Rearrangement of Cinnamaldehyde Anil Hydrochloride (10).** This hydrochloride rearranges readily upon heating in DMSO solution: heating a 0.6 M solution of **10** in DMSO at 100 °C for 3 h leads to complete consumption of **10**. After 3 h at 60 °C such a solution had only 25% of **10** remaining. At 25 °C the reaction of **10** proceeded only slowly.

The reaction products were isolated by pouring the reaction mixture or an aliquot from a kinetic run into an aqueous solution of NaOH. (Basic hydrolysis was necessary, in order to avoid the acid-catalyzed hydrolysis of the anil.) The hydrolysate was then extracted with three portions of ether and the combined ether extracts reextracted with water. The ether extracts were dried over anhydrous $MgSO_4$ and then evaporated. The residue was then analyzed by TLC, GC, or HPLC techniques. The preparative

(24) Eisch, J. J. *Organometallic Syntheses*; Academic Press: New York, 1981; Vol. 2, pp 7–20.

(25) Meyers, A. I. Heterocycles in Organic Synthesis; John Wiley & Sons: New York, 1974; p 204.

(26) Glinka, J. *Rocz. Chem.* **1965**, *39*, 885; *Chem. Abstr.* **1966**, *64*, 3470f.

separation of products was accomplished by column chromatography on silica gel, using eluents of a hexane–toluene mixture (25/75 v/v), toluene, and finally methanol. Fractions collected from the column were monitored by UV spectrophotometry.

The principal cyclic product isolated from the reaction of **10** was 2-phenylquinoline (**11**), mp 83–84 °C (35%) (lit.[27] mp 83–84 °C), which was identified by a spectral and melting point comparison with an authentic sample. No indication of the presence of 4-phenylquinoline was obtained. Depending upon the extent of reaction, small amounts of anil **9** and traces of cinnamaldehyde and aniline were also detected.

The other principal product was *N*-cinnamylaniline (**13**) (30%). This compound was identified on the basis of its spectral and analytical data and its synthesis by the reduction of **10** in DMSO solution by $NaBH_4$. Thus, a solution of 105 mg (2.7 mmol) of sodium borohydride in 15 mL of dry DMSO was slowly treated with 250 mg (1.03 mmol) of **10**. After 30 min the mixture was diluted with water and extracted with ether. Drying of the ether extract, evaporation of the ether, and HPLC analysis of the residue showed it to be >90% **13**. A pure sample was isolated by preparative HPLC.

Compound **13**: $^1H$ NMR ($CDCl_3$) 3.6 (br s, H–N), 3.97 (d, H, $J$ = 4 Hz), 6.5–7.0 (m, 5 H), and 7.3–7.6 (m, 7 H); IR (neat) 3440 $cm^{-1}$; MS (70 eV) 209 (P, 31) and 117 (100). This compound has been prepared previously from cinnamyl bromide and aniline.[28]

By allowing samples of **10** to reflux as a suspension in dry toluene or as a solution in acetonitrile and then hydrolyzing under basic conditions, 2-phenylquinoline and *N*-cinnamylaniline were also shown to form. Furthermore, addition of 1 molar equiv of water to a 0.6 mL solution of **10** in DMSO seemed to retard slightly the rate of reaction of **10** rather than accelerate the decomposition of **10**.

**Thermal Rearrangements of the Hydrochlorides of *N*-(*p*-Methylcinnamylidene)-*p*-toluidine (16) and *N*-Cinnamylidene-*p*-toluidine (17).** Analogous to the reaction of **10**, these hydrochlorides were individually allowed to react in DMSO between 70 °C and 90 °C and the reaction mixtures worked up in a similar manner.

From **17**, the expected quinoline 6-methyl-2-*p*-tolylquinoline was obtained, mp 39–40 °C: $^1H$ NMR ($CDCl_3$) 2.33 (s, 3 H), 2.45 (s, 3 H), 6.8–8.1 (m, 7 H); IR (neat) 1600 (s), 1495 (s), 825 (s), 800 (s), and 565 (s) $cm^{-1}$; MS (70 eV) 233 (P, 100), 218 (21, P – $CH_3$).

In addition, the reduced anil, *N*-(*p*-methylcinnamyl)-*p*-toluidine, was isolated and identified by $^1H$ NMR, IR, and MS data.

Likewise, from **16**, the formation of 6-methyl-2-phenylquinoline ($^1H$ NMR ($CDCl_3$) 2.5 (s, 3 H), 7.2–7.8 (m, 5 H), and 7.9–8.3 (m, 5 H); MS (70 eV) 219 (P, 100), 204 (19, P – $CH_3$)) and *N*-cinnamyl-*p*-toluidine ($^1H$ NMR ($CDCl_3$) 2.25 (s, 3 H), 3.6 (br s, H), 3.8 (d, 2 H, $J$ = 4 Hz), 6.3–6.6 (m, 4 H), and 6.9–7.3 (m, 5 H)) was observed.

(27) Colonna, M.; Risaliti, A. *Gazz. Chim. Ital.* **1953**, *83*, 58; *Chem. Abstr.* **1954**, *48*, 8784.
(28) Hurd, C. D.; Jenkins, W. W. *J. Org. Chem.* **1957**, *22*, 1418.

**Exchange between the Hydrochlorides of Cinnamaldehyde Anil (9) and *N*-(*p*-Methylcinnamylidene)-*p*-toluidine (15).** A solution of 2.0 mmol each of **10** and of **17** in 60 mL of dry DMSO was made up and allowed to stand for 5 min at 25–30 °C. Quenching with aqueous, alkaline workup and analysis by HPLC showed the presence of approximately equal amounts of **9**, **15**, *N*-cinnamylidene-*p*-toluidine (**14**), and a fourth component whose $^1H$ NMR and mass spectrum were consistent with the structure being *N*-*p*-cinnamylidene-*p*-toluidine (**22**).

Admixing 2.0 mmol each of the free Schiff bases **9** and **15** in 60 mL of dry DMSO and allowing the resulting solution to stand for 48 h at 25–30 °C led only to the unexchanged anils, **9** and **15**, upon hydrolytic workup.

**Exchange between Cinnamaldehyde Anil Hydrochloride (10) and *p*-Toluidine.** Admixing 2.0 mmol of **10** and 2.0 mmol of *p*-toluidine in 60 mL of dry DMSO for 5 min at 25–30 °C and then subjecting the mixture to a basic hydrolytic workup yielded a mixture of cinnamaldehyde anil, *N*-cinnamylidene-*p*-toluidine, *p*-toluidine, and aniline.

**Kinetics of the Thermal Rearrangement of Cinnamaldehyde Anil Hydrochloride (10).** A typical kinetic run employed an initial solution of 487 mg (2.0 mmol) of cinnamaldehyde anil hydrochloride in 30.0 mL of anhydrous DMSO. The solution was placed in a two-necked Schlenk vessel maintained under nitrogen, one neck of which was provided with a rubber septum. The temperature of the reaction mixture was maintained at 64.0 ± 0.1 °C in a constant-temperature bath and aliquots were withdrawn for analysis by a gas-tight syringe at 15-min intervals. Such samples were subjected to basic hydrolysis as described above for the rearrangement of **10**. The amounts of remaining starting anil **9** and products **10** and **13** were determined by HPLC techniques with the use of internal and external standards. The results of a typical kinetic run are given in Table I.

An interesting comparison was made of the rates at which 2-phenylquinoline was formed from a solution of pure **10** in DMSO and from an equimolar solution of **10** and **9** in DMSO. Thus, in one Schlenk vessel were placed 487 mg (2.0 mmol) of pure **10** in 30 mL of DMSO; in a similar vessel were admixed 243.5 mg (1.0 mmol) of pure **10** and 207 mg of **9** in 30 mL of DMSO. Both vessels were placed simultaneously in a constant-temperature bath at 64.0 ± 0.1 °C and aliquots withdrawn and analyzed for 2-phenylquinoline. The rate of formation of 2-phenylquinoline for the solution of **1** and **9** was approximately 20% faster than that for the solution of pure **10** (Table II).

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**Registry No.** **1**, 62-53-3; **2** (R = Ph), 14371-10-9; **5**, 52944-37-3; **10**, 118714-23-1; **11**, 612-96-4; **13**, 92573-86-9; **14**, 118714-21-9; **15**, 118714-22-0; **16**, 118714-24-2; **17**, 118714-25-3; **19**, 118714-26-4; **22**, 118714-28-6; **25**, 118714-27-5; TolCH=CHCHO, 56578-35-9; *p*-toluidine, 106-49-0; 6-methyl-2-phenylquinoline, 27356-46-3.