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KINETICS AND MECHANISM OF THE FORMATION OF 4-HYDROXYQUINOLINE FROM METHYL ANTHRANILATE*

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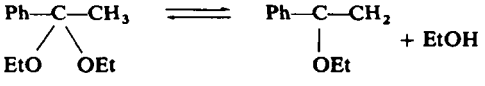
Abstract—The condensation of methyl anthranilate with α-ethoxystyrene to form 2-phenyl-4-hydroxyquinoline has been studied. Acetophenone diethyl ketal gives below 200° reversibly α-ethoxystyrene, which reacts below 190° readily with methyl anthranilate to afford α-methylbenzylidene-*o*-carbomethoxyaniline (I). The formation of 2-phenyl-4-hydroxyquinoline (III) by heating the Schiff base (I) at 250° is rate-determining and the rate of reaction is expressed as $v = k$ [Schiff base] [2-phenyl-4-hydroxy-quinoline]. This autocatalysis is a kind of acid catalysis, since *p*-toluic acid also catalyses effectively, but quinoline retards the reaction.

THE yield of 2-phenyl-4-hydroxyquinoline by heating anthranilic acid with acetophenone at 120° for two days by the original Niementowski synthesis is low (3–5%).[1] Fuson and Burgess improved the yield to 84% by heating ethyl anthranilate and acetophenone diethyl ketal at 250°; they explained the higher yield by the suppression of decarboxylation of anthranilic acid and also by the intermediary formation of α-ethoxystyrene from the ketal.[2] There seems, however, to be no evidence for the formation of α-ethoxystyrene and its reactivity higher than acetophenone itself. To clarify the mechanism, the reaction of α-ethoxystyrene with methyl anthranilate was studied stepwise in diphenyl ether, which confirmed the Schiff base formation and acid-catalysed cyclisation to a hydroxyquinoline derivative.

RESULTS AND DISCUSSION

Formation of α-ethoxystyrene from acetophenone diethyl ketal. Refluxing acetophenone diethyl ketal (b.p. 212–216°) for 22 hr gives no appreciable change in its IR spectrum, but heating below 200° with occasional removal of EtOH under reduced pressure readily affords α-ethoxystyrene, which indicates the reversibility of the reaction (1).



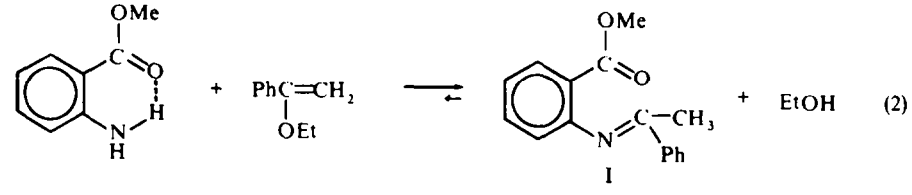
(1)

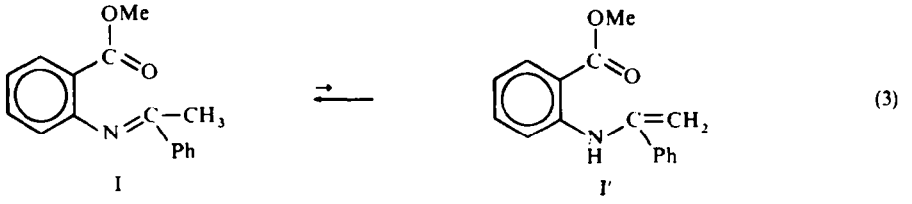
Under the same conditions α-ethoxystyrene did not afford phenylacetylene, since no appreciable IR band assigned to C≡C (2200–2300 cm^{-1}) was observed by the reaction.

* Contribution No. 155.

Generally, the ketals of the type $RC(OMe)_2CH_3$ are readily cleaved into vinyl ethers by heating with a small amount of acid.[3] The reversibility is also supported by a facile exchange of alkoxy group in α-alkoxystyrenes with foreign alcohols via mixed ketals.[3]

Reaction between α-ethoxystyrene and methyl anthranilate below 190°. Heating a mixture of α-ethoxystyrene and methyl anthranilate at 190° without solvent with occasional removal of EtOH under reduced pressure gave a Schiff base, i.e., α-methylbenzylidene-*o*-carbomethoxyaniline (I) quantitatively. The absorbances of IR spectrum before and after the reaction showed a remarkable decrease at 3370 cm^{-1} and 3480 cm^{-1} (νNH_2), 1700 cm^{-1} (ν C=O). 1630 cm^{-1} (ν C=C) and 800 cm^{-1} (δ =CH_2) together with the appearance of strong new peaks at 1730 (ν C=O) and 1650 cm^{-1} (ν C=N). The shift in CO frequency from 1700 cm^{-1} to 1730 cm^{-1} can be explained by the disappearance of strong chelation in the original methyl anthranilate. For example, methyl N-methylanthranilate shows the CO frequency of 1685 cm^{-1}, indicating the presence of a strong H-bond, while the CO frequency of methyl N,N-dimethyl-anthranilate reverts to the normal ester value of 1730 cm^{-1}.[4] Relative intensities at 1060 cm^{-1} (ν C—O) and 970 cm^{-1} of α-ethoxystyrene indicates almost complete conversion of methyl anthranilate into the Schiff base (I) and the shift of imine-enamine equilibrium (Eq 3) to the imine side. Distillation *in vacuo* gave I which was identified by the IR and NMR spectra. The reaction occurred also at 120°.





Acetophenone, however, did not react with methyl anthranilate under the same conditions as α-ethoxystyrene, since heating at 190° for 2 hr showed no appreciable change in IR spectrum and no indication of the presence of I.

Heating the mixture of α-ethoxystyrene and methyl anthranilate or the Schiff base I in boiling diphenyl ether (252°) readily gave 2-phenyl-4-hydroxy-quinoline (III), so that the formation of I may be an initial step of the reaction at lower temperature. Removal of the produced EtOH *in vacuo* at this stage enhanced slightly the formation of the hydroxyquinoline. This is explicable by the suppression of ketal formation, a reverse reaction in Eq. 1. Furthermore, unreacted α-ethoxystyrene might be converted into butyrophenone by heating at 250°,[5] which would result in a lower yield.

When diethyl ketals are refluxed with primary amines, Schiff bases are obtained,[6] probably via substituted vinyl ethers.[3]

Kinetics of the formation of 2-phenyl-4-hydroxyquinoline from the Schiff base. As stated above, the second stage of reaction is the formation of 2-phenyl-4-hydroxyquinoline (III) which requires higher temperature. Since α-methylbenzylidene-*o*-carbomethoxyaniline (I) is an intermediate, a mixture of α-ethoxystyrene and methyl anthranilate, which had been previously converted into I at 130°, was heated at 252° in diphenyl ether. The conversion curve is S-shaped (Fig 1a), suggesting autocatalysis, which was confirmed by the rate enhancement on addition of the product.

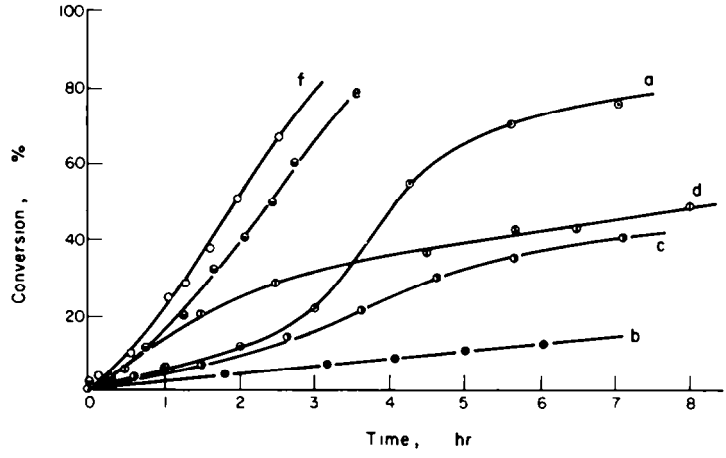


FIG 1. The effect of acids and bases for the formation of 2-phenyl-4-hydroxyquinoline. a, none; b, potassium hydroxide, 0·19M; c, quinoline, 0·22M; d, sulphuric acid, 0·008M; e, 2-phenyl-4-hydroxyquinoline, 0·081M; f, *p*-toluic acid, 0·085M

The data satisfied autocatalytic second-order kinetics[7] up to conversion over 80%.

$$\frac{d[III]}{dt} = k[\alpha\text{-ethoxystyrene}][III] \quad (4)$$

However, assuming that most of α-ethoxystyrene is converted into the Schiff base (I) at the primary stage, the rate of formation of the product (III) may be expressed as $v = k[I][III]$. The assumption is reasonable from the fact that a mixture of α-ethoxystyrene and methyl anthranilate is readily converted into III which can be distilled below 170° without cyclisation, and that the product mixture gives virtually the same IR and NMR spectra as those of purified α-methylbenzylidene-*o*-carbomethoxyaniline (I).

The rate constants are shown in Table 1. The effect of various acids and bases on the rate is shown in Fig. 1. *p*-Toluic acid showed striking rate enhancement, while quinoline resulted in retardation. Suphuric acid also showed rate enhancement at an early stage of reaction, but a considerable amount of polymeric substance was produced. Potassium hydroxide gave rise to remarkable retardation. In view of these

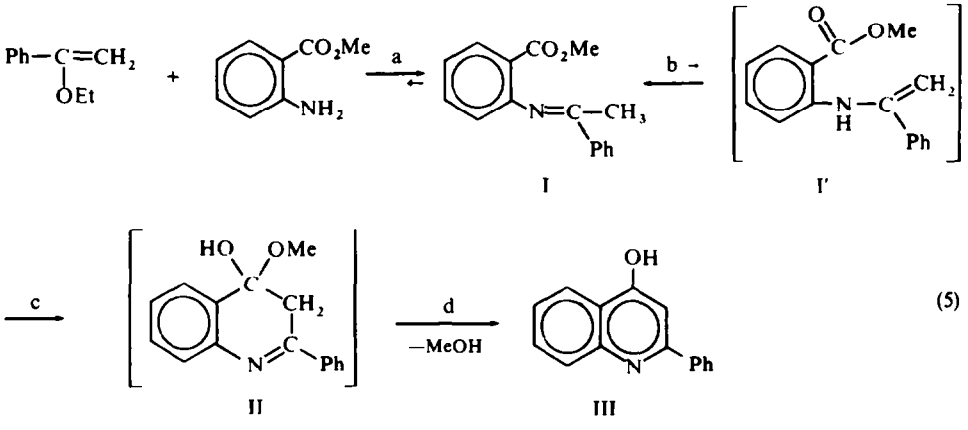
TABLE 1. SECOND-ORDER RATE CONSTANTS FOR THE FORMATION OF 2-PHENYL-4-HYDROXYQUINOLINE IN DIPHENYL ETHER AT 252°

$[A]_0$[a] M	$[S]_0$[b] M	$[P]_0$[c] M	$10^4 k_2$[d] M^{-1} sec^{-1}
0·648	0·517	0	4·33
0·633	0·519	0·0223	4·93
0·654	0·516	0·0810	4·32

[a] Methyl anthranilate
[b] α-Ethoxystyrene
[c] 2-Phenyl-4-hydroxyquinoline added initially
[d] Second-order rate constant in α-ethoxystyrene and in 2-phenyl-4-hydroxyquinoline

results, autocatalysis by III is a sort of acid catalysis. The catalysis by more acidic *p*-toluic acid is more effective than that by III.

Mechanism. A probable scheme consistent with the above observations is as follows.

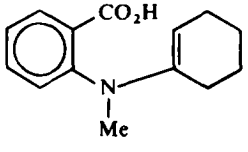


(5)

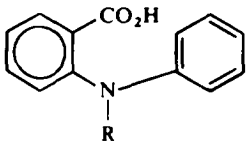
Cleavage of the ketal in Eq 1 and condensation of ethoxystyrene with the anthranilate in step a occur readily below 200°, while the overall reaction requires heating to 250°, hence step b, c or d may be rate-determining step. Kinetics alone cannot indicate the slower step. However, step b involves a simple prototropy which is ordinary rapid and step d involves the elimination of alcohol from hemiacetal which is generally liable to release alcohols even at room temperature. Hence, step c seems to be rate-determining.

Since bases retard the reaction, ethylene carbanion mechanism is unlikely for cyclisation. The cyclisation may involve an enamine intermediate (I'), a tautomer of the Schiff base (I). Such an intermediate (IV) like I' was postulated for the condensation of cyclohexanone with N-methylanthranilic acid which cannot form azomethine linkage to give N-methyl-1,2,3,4-tetrahydroacridone.[8] Moreover, some diarylamine-2-carboxylic acids or esters (V) which can be regarded as enamines can cyclise to give acridones in good yields.[9]

These cyclocondensations require heating to 220–320° as in the present reaction, and in some cases $POCl_3$ was used as catalyst. On the other hand, the Friedländer synthesis involving *o*-aminobenzaldehyde or *o*-aminophenyl ketone occurs more easily, i.e., on heating to 120–200°[10], which reflects stronger electrophilicity of the CO group than of the carboxyl group.



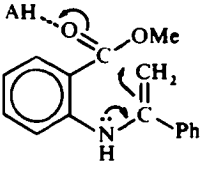
IV



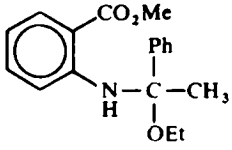
R = H, COPh

V

An attack of the methylene C atom on the carbonyl C atom in step c is subject to acid catalysis (VI), where weak acid such as *p*-toluic acid and 2-phenyl-4-hydroxyquinoline is effective.



VI



VII

An addition-elimination mechanism involving the tetrahedral intermediate (VII) is most probable for the formation of I from the reaction of α-ethoxystyrene with methyl anthranilate. Any other mechanism is less plausible as will be stated. An elimination-addition mechanism via phenylacetylene as an intermediate is ruled out since α-ethoxystyrene is not converted into phenylacetylene under the reaction conditions, i.e., on heating at 190° under reduced pressure (IR analysis, see above). A mechanism involving acetophenone which is the hydrolysis product of α-ethoxystyrene is also excluded since acetophenone forms virtually no Schiff base I under the reaction conditions. An alternative mechanism involving a vinylic cation seems unlikely because alkoxide is one of the weakest leaving groups and ethoxystyrene has no substituent favourable for the cation formation.[11]

EXPERIMENTAL

Materials. α-Ethoxystyrene was prepared by heating acetophenone diethyl ketal below 200° under reduced pressure to remove EtOH, and rectified three times to remove acetophenone and its ketal, b.p. 71–2°/2 mm, 96·7% pure by GLC analysis. These contaminative ketones and ketal do not affect kinetics. Commercial methyl anthranilate of reagent grade was used.

α-Methylbenzylidene-2-carbomethoxyaniline (I). In a flask equipped with a reflux condenser circulated by water of 70–80° a mixture of α-ethoxystyrene (0·0066 mole) and a small excess methyl anthraniliate (0·0077 mole) was heated at 190° for 2 hr with occasional expulsion of EtOH under reduced pressure. IR spectra in liquid film of a mixture were compared before and after the reaction. Peaks of α-ethoxystyrene at 1630 cm^{-1} (ν C=O), 1060 cm^{-1} (ν C—O), 970 cm^{-1} and 800 cm^{-1} (δ $=CH_2$) were almost completely disappeared after the reaction; peaks of methyl anthranilate at 3480 cm^{-1} and 3370 cm^{-1} (ν NH_2), 1700 cm^{-1} (ν C=O) and 1105 cm^{-1} were decreased remarkably. Instead, some new peaks appeared at 1700 cm^{-1} (ν C=O) and 1650 cm^{-1} (ν C=N), 1210 cm^{-1}, 1080 cm^{-1}, 830 cm^{-1} and 730 cm^{-1} after the reaction. The product was pale yellow liquid and the fraction boiling at 162–166°/4 mm was collected. The IR

spectrum of the purified material showed characteristic peaks of I. The NMR spectrum showed signals for the Me protons at τ 7·9 singlet; for the OMe protons at τ 6·3, singlet; for the protons of both aromatic rings at τ 2·0–3·4, complex. It is sensitive to moisture and liable to hydrolysis on exposure to air.

Acetophenone instead of α-ethoxystyrene is similarly heated with methyl anthranilate at 190° for 2 hr, but no reaction occurred, the reactants being recovered. The reaction mixture showed no change of IR spectrum during the reaction.

Product criterion. A diphenyl ether soln of α-ethoxystyrene (0·5 M) and methyl anthranilate (0·6 M) was heated at 120–130° for 2·5 hr with occasional expulsion of EtOH *in vacuo* under slow flow of N_2. After EtOH was expelled, the soln was heated to 252° to reflux. The soln after 10 hr refluxing gave on cooling a ppt of 2-phenyl-4-hydroxyquinoline in the 70–90% yield. Recrystallised from EtOH, m.p. 258–260°. That 4-hydroxyquinolines have tautomers and exist predominantly as oxo forms is well established[12] but in this report we do not differentiate the hydroxy form from the oxo form. UV spectral data (λ_{max} in nm and log ε) were as follows: 335 (3·77), 247 (3·88), 218 (4·47) in MeOH; 315 (4·27), 265 (4·48) and 230 (4·29) in methanolic H_2SO_4.

Kinetic procedure. The reaction was carried out as described above, where the reaction temp was maintained at 252 ± 1° throughout the run. Aliquots were pipetted out and diluted with MeOH. After addition of one drop of H_2SO_4 the soln was analysed UV spectrophotometrically. Extinction at 315 nm of 2-phenyl-4-hydroxyquinolinium ion was followed, where α-ethoxystyrene, methyl anthranilate and diphenyl ether had no appreciable absorption. A conversion curve was S-shaped, as shown in Fig 1a, and fitted the autocatalytic second-order rate expression[7]: $dx/dt = k(a - x)(b + x)$, where k is a second order rate constant, b is the initial concentration of added 2-phenyl-4-hydroxyquinoline and a is that of α-ethoxystyrene.

IR spectra were recorded on a Perkin–Elmer grating spectrophotometer model 337, UV spectra on a Hitachi spectrophotometer model 124 and GLC on a Yanagimoto gas chromatograph model 550 F with a 1 m column packed with 5% PEG 20M on Celite CS.

REFERENCES

[1] S. V. Niementowski, *Ber. Dtsch. Chem. Ges.* **27**, 1394 (1894); R. H. Manske, *Chem. Revs* **30**, 127 (1942)
[2] R. C. Fuson and D. M. Burgess, *J. Am. Chem. Soc.* **68**, 1270 (1946)
[3] D. B. Killian, G. F. Hennion and J. A. Nieuland, *Ibid.* **57**, 544 (1935)
[4] R. S. Rusmussen and R. R. Brattain *Ibid.* **71**, 1073 (1949)
[5] K. B. Wiberg and B. I. Rowland, *Ibid.* **79**, 1159 (1955)
[6] L. Claisen, *Ber. Dtsch. Chem. Ges.* **29**, 2931 (1896); P. Y. Sollenberger and R. B. Martin, *The Chemistry of the Amino Group* p. 357. Interscience, New York (1968)
[7] K. B. Wiberg, *Physical Organic Chemistry* p. 320. Wiley, New York (1963)
[8] R. A. Reed, *J. Chem. Soc.* 425 (1944)
[9] M. M. Jamisen and E. E. Turner, *Ibid.* 1954 (1937); J. W. Schulenberg and S. Archen, *Organic Reactions* Vol. 14; p. 15. Wiley, New York (1965)
[10] E. A. Fehnel, *J. Org. Chem.* **31**, 2899 (1966)
[11] Z. Rappoport and A. Gal, *J. Am. Chem. Soc.* **91**, 5246 (1969)
[12] A. R. Katritzky and J. M. Lagowski, *Advances in Heterocyclic Chemistry* Vol. 1; p. 312 Academic Press, New York (1963)