Enamine Formation from Anilines and Methyl Propiolate. The Synthesis of 4(1*H*)-Quinolones (1)

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The addition of substituted anilines to methyl propiolate produces labile *cis-trans* mixtures of enamines which can be isomerized by acid, solvent variation, and thermal techniques. Thermal cyclization of these enamines provides a synthesis of 4(1*H*)-quinolones.

As part of a program aimed at the synthesis of a series of 4,8-diaminoquinolines for evaluation as anti-malarial agents, we reviewed the methods available for the synthesis of 4-quinolones, the convenient precursors of 4-aminoquinolines. Published routes to 4-quinolones include the reaction of arylamines with β-dicarbonyl compounds (the Conrad-Limpach reaction) (3), with diethyl ethoxymethylenemalonate (the Gould-Jacobs reaction) (4) and with dimethyl acetylenedicarboxylate (5). These methods, however, are made somewhat lengthy by the saponification and decarboxylation procedures required to generate 4-quinolones from the initially formed 2(or 3-)-carboalkoxy-4-quinolones. Obviously the reaction would be simplified if these stages could be avoided. With this aim in view, Price (6) ring-closed 3-anilinoacrylates which he prepared from anilines and sodio formylacetate. Although this reaction produced 4-quinolones directly in the cyclization step, the convenience of the method was reduced by the low yield in the condensation stage and by the general inconvenience of handling aqueous solutions of sodio formylacetate of unknown concentration. A variation of this method was proposed in which the anilinoacrylate was prepared by the nucleophilic addition of anilines to methyl propiolate (7), but the reaction was applied to only one amine, *m*-chloroaniline and was not further investigated. As the latter route appeared to be the most promising general method of preparing 4-quinolones, we decided to investigate the scope of the reaction.

Preparation of the Anilinoacrylates.

Table I lists the yields, isomer ratios, melting points and analyses of the crystalline 3-anilinoacrylates, prepared by mixing equimolar amounts of the anilines and methyl propiolate in methanol. In all cases except those noted below, the reactions were exothermic and were completed after standing at room temperature for 12 hours. Single recrystallizations from methanol gave analytically pure materials (usually of mixed *cis* and *trans* isomers). *p*-Nitroaniline reacted only very slowly at room temperature, and even after heating at 40° for a week, a minimal conversion to the corresponding acrylate was obtained. Reaction at higher temperatures was precluded by the demonstrated instability of the adducts to prolonged heating. *o*-Nitroaniline gave no isolable yield of adduct after several weeks. The reaction of 3,5-dichloroaniline was also sluggish but a 40% yield could be obtained after standing at room temperature for 10 days.

Stereochemistry and Isomerization of the Adducts.

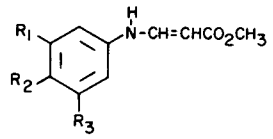
The isomer ratios of the adducts were determined by NMR spectroscopy in DMSO-d_6 stored over anhydrous potassium carbonate (8). The proton alpha to the ester function could be cleanly integrated in the *cis*- and *trans* acrylate isomers as an indication of the isomer balance. For the *cis*-acrylates the proton appeared at δ 4.77 ± 0.11 ppm and for the *trans* products at 5.17 ± 0.09 ppm. These protons were typical AB doublets with J = 8.5 Hz for the *cis* and 13.5 Hz for the *trans* cases. The *p*-nitroaniline adduct represented a special case and its alpha proton appeared at δ 5.03 ppm in *cis* and 5.44 ppm in *trans*.

The preparative reactions (Table I) were all carried out at such concentrations that the adducts precipitated. Under these conditions, the isolated isomer ratio will depend upon the relative solubilities of the isomers, the rate of the reaction and the rate of isomerization in solution. Thus any interpretations about the addition mechanism based on the isomer distribution in the isolated material would be tenuous.

From examination of the behavior of *cis* and *trans* methyl 3-anilinoacrylates, we were able to establish the

TABLE I

Methyl 3-Anilinoacrylates

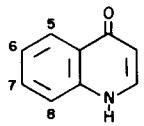


Compound	R_1	R_2	R_3	Yield %	*Cis/Trans* (a) %	M.P. °C	Formula	Calcd. % C	H	N	Found, % C	H	N
I	H	H	H	70	0/100	146-148 (b)	$C_{10}H_{11}NO_2$	67.76	6.26	7.91	67.69	6.31	7.90
II	H	MeO	H	76	0/100	162-164 (c)	$C_{11}H_{13}NO_3$	63.75	6.32	6.76	63.86	6.43	6.74
III	H	NO_2	H	14	100/0	185-187	$C_{10}H_{10}N_2O_4$	54.05	4.53	12.61	53.85	4.33	12.58
IV	H	Cl	H	72	50/50	172-173 (d)	$C_{10}H_{10}ClNO_2$	56.75	4.76	6.62	56.61	5.07	6.61
V	H	F	H	50	50/50	127-135	$C_{10}H_{10}FNO_2$	61.53	5.16	7.17	61.76	5.17	7.11
VI	H	I	H	58	65/35	159-161	$C_{10}H_{10}INO_2$	39.63	3.33	4.62	39.84	3.52	4.63
VII	Cl	OMe	H	76	60/40	106-108	$C_{11}H_{12}ClNO_3$	54.67	5.01	5.79	54.40	4.87	5.69
VIII	Cl	H	Cl	40	(e)	90-1	$C_{10}H_9Cl_2NO_2$	48.81	3.69	5.69	48.52	3.97	5.43

(a) Based on all crystalline material isolated from the reaction mixture assayed by NMR. The melting points are of the analytically pure product which does not in all cases contain the same *cis/trans* balance (exception noted). (b) Lit. (8), m.p. 148-149°. (c) Lit. (8), m.p. 162-165°. (d) Upon recrystallization only *trans* material was isolated. (e) Material was too insoluble to obtain NMR spectrum.

TABLE II

4-Quinolones



	Compound	Yield %	M.P. °C	Calcd. %			Found %		
				C	H	N	C	H	N
IX	Unsubstituted	42	209-211 (a)	74.46	4.86	9.65	74.17	4.61	9.57
X	6-MeO	47	250-252 (c)	68.56	5.18	7.99	68.31	4.96	7.99
XI	6-NO_2	18	337-342 (dec.)	56.84	3.18	14.73	56.88	3.31	14.50
XII	6-Cl	65	269-271 (b)	60.19	3.37	7.80	59.85	3.40	7.70
XIII	6-F	58	222-224 (d)	66.24	3.71	8.58	66.38	3.89	8.35
XIV	6-I	44	267-275 (dec.)	39.87	2.24	5.17	39.82	2.24	5.11
XV	5,7-diCl	65	348-350 (dec.)	50.50	2.35	6.54	50.76	2.50	6.30

(a) Lit. m.p. 214°, B. Riegel, G. R. Lappin, B. H. Adelson, R. I. Jackson, C. J. Albisetti, Jr., R. M. Dodson, and R. H. Baker, *J. Am. Chem. Soc.*, 68, 1264 (1946). (b) Lit. m.p. 274-275°, *ibid.*, (c) Lit. m.p. 237-238°, A. R. Surrey and H. F. Hammer, *ibid.*, 68, 113 (1946). (d) Lit. m.p. 221-223°, H. R. Snyder, H. E. Freier, P. Kovacic, and E. M. Van Heyningen, *ibid.*, 69, 371 (1947).

lability of the enamine isomers. Thus, addition of traces of chloroacetic acid to an acid-free deuteriochloroform solution of *trans* or *trans*-containing acrylates effected a complete transformation to *cis* in less than a minute. A much slower acid catalyzed isomerization could be observed in DMSO. Huisgen has already noted that the *trans*-to-*cis* conversion is spontaneous and does not require the presence of acids; even in acid-free benzene complete *trans*-to-*cis* conversion occurred in a matter of days (8).

An opposite effect can be noted in methanol. We have observed that any isomer mixture which is recrystallized from methanol tends to isomerize toward increasing *trans* content. A sample of 33% *trans*/67% *cis* methyl 3-anilinoacrylate was dissolved in a minimum of hot methanol, evaporated to dryness in a vacuum and examined in the NMR (DMSO-d_6). It was possible to observe a steady increase in the *trans* content to 89% after four such treatments. Even the presence of an equimolar quantity of methanol diluted by DMSO (3:1 excess DMSO) catalyzed a slow *cis*-toward-*trans* isomerization at ambient temperatures. A synthetic mixture of 37% *trans*/63% *cis* shifted over a three-week period to 50% *trans* content.

A tentative explanation for the above observations rests on the assumption that the greater stability of the *cis* acrylates (in nonmethanolic solvents) arises from the intramolecular NH· · ·O=C hydrogen bond. In alcoholic media intermolecular association with solvent disrupts the chelative hydrogen bond and permits formation of the more sterically favored *trans* enamine system. Certainly there is ample evidence for strong intramolecular stabilization in the *cis* enamines. Our NMR spectra show the NH resonances some 0.2 to 0.3 ppm downfield in *cis* vs. *trans* isomers, an affect which correlates nicely with the deshielding influence of the hydrogen-bonded ester carbonyl in *cis* isomers.

Cyclization of the Adducts to 4-Quinolones.

All of the cyclizations were performed in boiling diphenyl ether essentially as described by Price (6). In order to avoid the production of undesired bimolecular side products, the cyclizations were performed in highly dilute solutions (20:1 w/w). The products were purified by sublimation and recrystallization. Table II gives the yields, melting points and analyses of the quinolones. The only case in which any difficulty was noted was in the cyclization of the nitro adduct III in which considerable decomposition back to the starting aniline was noted.

The *cis*/*trans* isomer ratio in the acrylate does not effect the cyclization to the quinolone. Various mixtures of the same acrylate gave comparable yields when treated under the same conditions. Indeed, it is apparent that *trans*-to-*cis* isomerization must preceed ring closure. A sample of pure *trans*-methyl 3-(*p*-chloroanilino)acrylate was held at its melting point, 175°, for 30 sec. The total material obtained on resolidification was examined in the NMR and was now found to be a 40/60 *cis*/*trans* mixture. More extensive thermal treatment resulted in partial cyclization and the thermal isomerization could not be followed in greater detail.

EXPERIMENTAL (9)

General Procedure for Preparation of Methyl 3-Anilinoacrylates.

The technique utilizing *p*-chloroaniline is reported as typical of the results obtained with the more reactive anilines.

Methyl 3-(*p*-Chloroanilino)-acrylate (IV).

A solution of *p*-chloroaniline (12.7 g., 0.10 mole) and methyl propiolate (8.4 g., 0.10 mole) in methanol (20 ml.) was allowed to react at room temperature overnight. *Cis,trans*-methyl 3-(*p*-chloroanilino)-acrylate (IV) (11.9 g., 56%), m.p. 160-165°, was collected by filtration. When this solid was dissolved in benzene and concentrated, the less soluble pure *trans* (IV), m.p. 172-173° could be obtained. The mother liquors from the reaction upon evaporation and recrystallization from methanol yielded an additional 3.2 grams of adduct. Although this more soluble material was largely *cis* isomer, pure *cis* material could not be obtained, total *cis* + *trans* yield, 72%.

Methyl 3-(*p*-Nitroanilino)-acrylate (III).

A solution of *p*-nitroaniline (6.9 g., 0.05 mole) and methyl propiolate (4.2 g., 0.05 mole) in methanol (50 ml.) was heated at 40° for 7 days. Upon cooling, *cis*-methyl 3-(*p*-nitroanilino)-acrylate (1.5 g., 14%) m.p. 180-183° crystallized and was collected by filtration. Recrystallization from methanol gave an analytical sample, m.p. 185-187°.

General Procedure for Quinolone Preparation. 6-Chloro-4(1*H*)-Quinolone (XII).

Diphenyl ether (20 ml.) was heated to reflux and 1.0 g. of IV was added. Reflux was continued for 15 minutes, and the solution was cooled and flooded with low-boiling petroleum ether. The precipitated 6-chloro-4(1*H*)-quinolone (XII) was filtered and dried *in vacuo*, 0.55 g., 65%, m.p. 258-263°. An analytical sample was prepared by sublimation *in vacuo* at 200° and 0.1 mm Hg. For analytical data and yields see Table II.

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(1a) This work was carried out under contract DA-49-193-MD-3011 from the U. S. Army Medical Research and Development Command and represents contribution number 532 from the Army research program on malaria. (b) Presented before the Organic Chemistry Division of the 156th National ACS Meeting, September 1968, Atlantic City, New Jersey. (c) For the previous contribution in this series see N. D. Heindel, T. F. Lemke and V. B. Fish, *J. Org. Chem.*, 33, 3997 (1968).

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