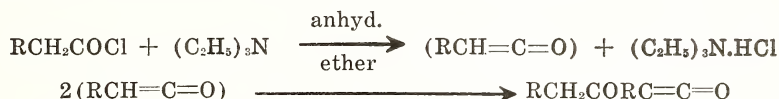


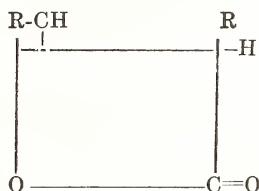
The Preparation of Several 3,4-Dialkylquinolines and Intermediate Compounds

D. J. COOK and WAYNE E. SCHELWALT,¹ DePauw University

Past studies have shown the use of diketene for the preparation of a number of substituted carbostyrils from aniline and the subsequent reduction of the carbostyrils to the corresponding quinolines. (1) (2) The present study involved the preparation of several alkylketene dimers which were then condensed with aniline to give the substituted acetoacetanilides and then converted to the 3, 4-dialkylcarbostyrils by an acid catalyzed ring closure. The various ketene dimers were prepared by the dehydrohalogenation of the corresponding acid chlorides.



The ketenes dimerize spontaneously on heating without isolation of the monomer. The accepted structure of the ketene dimers is the cyclic lactone.



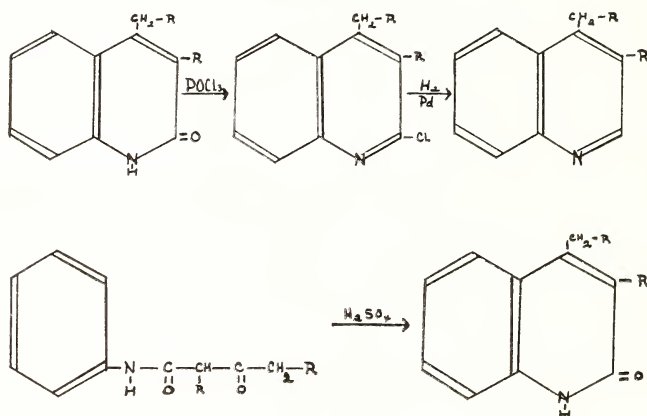
The alkylketene dimers were prepared according to the method of Sauer (3) and are listed in Table 1.

The ketene dimers were condensed with equimolar quantities of aniline by dropwise addition of the dimer to the amine at a temperature of 110°C and subsequent heating of the mixture for three to four hours at a temperature of 130°C. The resulting α , ν -dialkylacetoacetanilides were purified by recrystallization from ethanol as white crystalline solids. They are listed in Table 2.

Ring closure of the substituted acetoacetanilides was completed by the method of Knorr (4). While acetoacetanilide ring closes under exothermic conditions, the substituted acetoacetanilides were much slower. Various amounts of sulfuric acid were employed and it was found that a four to one ratio of sulfuric acid to the substituted acetoacetanilide by weight gave the best results. With an increasing carbon chain length of the substituted acetoacetanilide side chains, ring closure was found to proceed best when the temperature of the reaction mixture was held lower than 85°C for α -propionylpropionanilide and no higher than 65°C for the higher chain length anilides.

¹Submitted to the Chemistry Department of DePauw University as a partial fulfillment of the Master of Arts Degree by Wayne E. Schelwalt, June, 1964.

Higher temperatures reduced the yield of the carbostyrils by 15-30%. The time of reaction varied from 15-20 minutes for the two smaller members of the series to 30-60 minutes for the two larger substituted acetoacetanilides. The 3, 4-dialkylcarbostyrils have the following general formula and are reported in Table 3.



By means of previous described methods (2) (5), the carbostyrils were converted to the 2-chloro-3, 4-dialkylquinolines and then reduced to the quinolines.

The carbostyrils were heated with a slight excess of phosphorus oxychloride at 85°C for approximately thirty minutes and the excess POCl_3 was destroyed in ice water. The 2-chloro-3, 4-dialkylquinolines were then recovered by extraction with ether, dried, and the other removed leaving oils. The two lower homologs of the series were crystallized from ethanol but the two higher members of the series could not be purified by crystallization nor could they be distilled without decomposition. These oils were again extracted with ether and dried. Upon evaporation of the ether, the oils were recovered. Although no physical constants were obtained, the oils were sufficiently pure for analysis. These compounds are listed in Table 4.

Although a variety of methods have been described for the reduction of 2-chloroquinolines to the quinolines (6) (2), palladium on carbon with low pressure hydrogenation was used to prepare the 3, 4-dialkylquinolines in this study. The time necessary to reduce these chloro-derivatives to the quinoline was much longer than that required for 2-chlorolepidine. The 2-chloro-3, 4-dialkylquinolines required a minimum of fifteen to twenty hours at pressures of thirty to thirty-five pounds. The quinolines prepared in this study are listed in Table 5.

The picrates of the substituted quinolines listed in Table 5 were prepared by the accepted method and identified. These compounds are listed in Table 6.

The principal infrared absorption spectra of these compounds have been summarized in Table 7. The absorption bands of each class of compounds are quite similar from one compound to the other. The

TABLE 1

Ketene Dimer R = CH ₃	Percent Yield	b.p. °C	Reported b.p. °C (3)
C ₂ H ₅	38	45-48/10 mm	57-58/12 mm
C ₃ H ₇	66	74-75/11 mm	95-96/32 mm
C ₄ H ₉	66	97-98/10 mm	135-36/30 mm
	40	121-22/ 8 mm	127-29/ mm

TABLE 2

Substituted Acetoacetanilides	Percent Yield	m.p. °C	Reported (3) m.p. °C
α -Propionylpropionanilide	77	118.5-119	—
α -Butyrylbutyranilide	85	84-85	84-85
α -Valerylvaleranilide	84	88-89	68-69
α -Caproylcaproanilide	83	84-85	76-77

TABLE 3

Carbostyryl R = CH ₃	m.p. °C	Percent Yield	Analysis Found			Analysis Calculated			Picrate m.p. °C
C ₂ H ₅	188.5-190	84	C	H	N	C	H	N	186-187.5
C ₃ H ₇	186-187	88	77.0	6.96	7.56	77.0	6.95	7.48	151-152
C ₄ H ₉	142	31	77.3	7.81	6.66	78.3	7.91	6.52	146-147
C ₆ H ₁₃	148-149	56	78.1	8.38	6.19	79.2	8.65	5.77	120-121
			78.7	9.50	5.32	79.7	9.24	5.17	

TABLE 4

2-Chloro-3, 4- dialkylquinolines	Percent Yield	m.p. °C	Analysis Found			Analysis Calculated		
R = CH ₃	90	71.5-72.5	C	H	N	C	H	N
C ₂ H ₅	100	87.5-88.5	70.0	5.99	6.75	70.2	5.85	6.82
C ₃ H ₇	81	oil	71.8	6.78	5.97	72.0	6.85	6.00
C ₄ H ₉	100	oil	73.5	7.50	5.85	73.5	7.65	5.36
			74.2	8.22	4.98	74.7	8.28	4.84

TABLE 5

Substituted Quinoline	Percent Yield	b.p. °C	N, Found	N, Calcd.
3-Methyl-4-ethyl- (I)	36%	154-156/10 mm	6.37	8.18
3-Ethyl-4-n-propyl (II)	40%	167-169/10 mm	7.25	7.04
3-n-Propyl-4-n-butyl (III)	63%	186-190/10 mm	6.37	6.17
3-n-Butyl-4-n-pentyl (IV)	61%	215-218/8.5 mm	5.49	5.78

TABLE 6

Picrate of	m.p. °C	Analysis Found			Analysis Calcd.		
		C	H	N	C	H	N
I	190-192	53.6	3.78	13.69	54.0	4.00	14.0
II	172-173	56.3	4.88	12.93	56.1	4.67	13.1
III	166-167	57.5	5.14	12.2	57.9	5.26	12.2
IV	137-139	59.8	6.06	11.5	59.5	5.78	11.6

TABLE 7

Infrared Spectra			Hydrogen Deformation	
Compound	Alkane CH (mull)	Aromatic CH (mull)	C=C and C=N	745-755 cm ⁻¹
3, 4-Dialkyl-carbostyryl			1550 cm ⁻¹ 1600 1500 1450	
2-Chloro-3, 4-dialkylquinoline	2850-2925cm ⁻¹	3050 cm ⁻¹	1550-1560cm ⁻¹ 1600 1500 1450	760 cm ⁻¹
3, 4-Dialkyl-quinoline	2850-2925cm ⁻¹	3050 cm ⁻¹	1640-1650 cm ⁻¹ 1550-1560 1600 1500 1450	760 cm ⁻¹

spectra of the carbostyrils are closely related to those already reported (7). Although a limited amount of data has been reported concerning the quinolines (8), agreement has been found between these compounds and the less highly substituted quinolines. However, where 2, 3- and 2, 4-dimethylquinoline show bands at $755\text{--}758\text{ cm}^{-1}$ for the four adjacent hydrogen in the homocyclic ring and a band at 864 cm^{-1} for the single heterocyclic hydrogen atom (9), it is of interest to note that the 3, 4-dialkylquinolines prepared in this study, show only a strong hydrogen deformation band near 760 cm^{-1} with no band appearing in the $860\text{--}900\text{ cm}^{-1}$ region which should be due to the single hydrogen in the 2 position of the hetero ring. In both types of compounds, 2-chloro-3,4-dialkylquinoline and 3,4-dialkylquinoline, there are common absorption bands at 922, 1060, 1162 and 1300 cm^{-1} but which have not been identified.

Experimental¹

Since each class of compounds were prepared by similar methods, only one illustration of each type will be described. The ketene dimers were prepared according to the method described by Sauer (3).

α -Propionylpropionanilide. Twenty-five grams (.268 moles) of aniline was heated to 110°C and 30 g. (.268 moles) of methylketene dimer was added dropwise with stirring over a period of thirty minutes. The mixture was then maintained at 130° for another three and one-half hours. After cooling, the mixture was dissolved in a small amount of alcohol and with the addition of water, light tan crystals formed. The weight of the product was 42.7 g. and melted at $118.5\text{--}119^{\circ}\text{C}$.

Anal. Calcd. for $\text{C}_{12}\text{H}_{15}\text{NO}_2$: C, 70.3; H, 7.78; N, 6.88

Found: C, 70.4; H, 7.60; N, 7.77.

Other compounds of this series are reported in Table 2.

3-Methyl-4-ethylcarbostyryl. Fifty-nine grams of concentrated sulfuric acid was heated to 75°C and over a twenty to thirty minute period, 14.7 g. (.0714 mole) of α -propionylpropionanilide was added to the acid with stirring. The reaction mixture was then heated to 85° for ten minutes and then poured into 600 ml of ice water and neutralized with aqueous sodium hydroxide. The crude product was recrystallized from ethanol and water. The yield was 11.2 g. and melted at $188.5\text{--}190^{\circ}\text{C}$. Details of these products are noted in Table 3.

2-Chloro-3-methyl-4-ethylquinoline. Nine and nine-tenth grams of 3-methyl-4-ethylcarbostyryl (.0529 moles) was heated in 9.73 g. (.0634 moles) of phosphorus oxychloride at $80\text{--}85^{\circ}$ for fifteen minutes. The hot solution was poured into 400 ml. of ice water and the precipitate extracted with ether and dried over anhydrous sodium sulfate. After removal of the ether, the product was recrystallized from ethanol and water. The product weighed 9.7 g. and melted at $71.5\text{--}72.5^{\circ}\text{C}$. These compounds are listed in Table 4.

3-Methyl-4-ethylquinoline. Eight grams (.0389 moles) of 2-chloro-3-methyl-4-ethylquinoline and 3.19 g. of anhydrous sodium acetate was dissolved in 100 ml of glacial acetic acid. Three grams of palladium on carbon catalyst was added to the solution and the mixture subjected to

¹All melting points and boiling points are uncorrected.

low pressure hydrogenation (30 pounds) at a temperature of 55-70°C for sixteen hours. The catalyst was removed by filtration and the acetic acid separated by vacuum evaporation at 70°C and 25 mm. The residue was poured into water and neutralized with sodium hydroxide. The aqueous suspension was extracted with ether, dried over anhydrous sodium sulfate, and the ether removed. The oil was distilled and 2.4 g. which boiled at 154-156°/10 mm was recovered. The product is a colorless, oily liquid with no distinct odor. Data concerning the prepared 3, 4-dialkylquinolines are found in Table 5 and the corresponding picrates are reported in Table 6.

Literature Cited

1. Cook, D. J., and W. C. Lawall, 1948. *J. Am. Chem. Soc.* **70**:1918.
2. Horning, E. 1955. *Organic Syntheses*. John Wiley and Sons, Inc., New York. Col. Vol. III: 194 and 519.
3. Sauer, J. C. 1947. *J. Am. Chem. Soc.* **69**:2444.
4. Knoor, L. 1886. *Ann.* **236**:110.
5. Mikhailov, G. I. 1936. *J. Gen. Chem. U.S.S.R.* 6:511, cited in *C.A.* 30:6372, (1936).
6. Krahler, S. E. and A. Burger. 1941. *J. Am. Chem. Soc.* **63**:2368.
7. Cook, D. J., R. S. Yunghans, T. R. Moore, and B. E. Hoogenboom. 1957. *J. Org. Chem.* **22**:211.
8. Bellamy, L. J. 1954. *Infra-red Spectra of Complex Molecules*. John Wiley and Sons, Inc. New York. 279.
9. Cook, G. L., and F. M. Church. 1957. *J. Phys. Chem.* **61**:458.