[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY]

The Synthesis of Some 4-Quinolinols and 4-Chloroquinolines by the Ethoxymethylenemalonic Ester Method[1]

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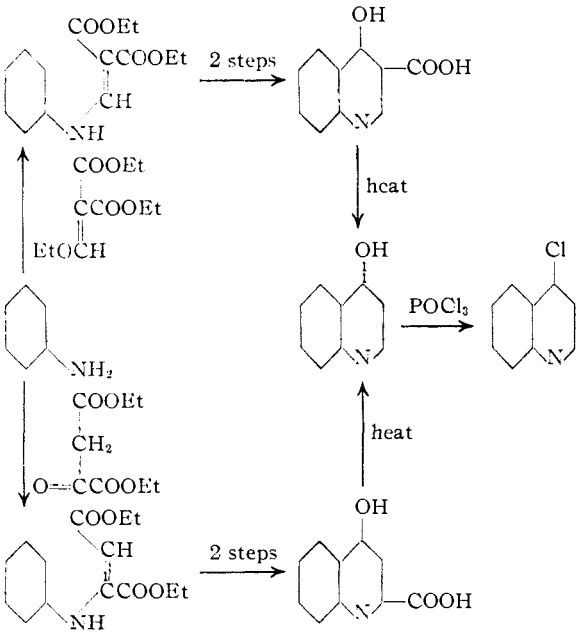
The preparation of 4-alkylaminoquinolines is most conveniently accomplished by coupling the appropriate amine with a 4-haloquinoline. In this Laboratory three principal methods have been investigated for the preparation of 4-haloquinolines. The Meisenheimer[2] procedure is not generally applicable and, for example, is entirely unsatisfactory as a method for the preparation of 4,7-dichloroquinoline and 4-chloro-8-quinolinesulfonic acid. The oxalacetic ester synthesis[3] is perhaps more general in application than the Meisenheimer but the cyclization and decarboxylation steps require conditions which vary widely depending upon the substituents in the carbocyclic ring. The most general method thus far developed is the ethoxymethylenemalonic ester synthesis. Ring closure of the anilinomethylenemalonic ester was first employed by Gould and Jacobs[4] to prepare 3-carboxy-4-quinolinol. The decarboxylation of this acid gives more uniform results than obtained with the 2-carboxy-4-quinolinol from the oxalacetic ester synthesis. This method of synthesis has been widely used among the antimalarial contractors and was developed principally by C. C. Price and co-workers at the University of Illinois.[5] A comparison of the two ring closure methods is presented.



The formation of the substituted anilinomethylenemalonic esters is very general and almost quantitative. In some large-scale operations the malonic esters are formed by preliminary heating of the reactants in Dowtherm A followed by a short period of heating to close the ring but in this work it has been customary to isolate them after preparation according to Claisen's original method.[6] The yields of 3-carbethoxy-4-quinolinols from this procedure are summarized in Table I and the analytical data and melting points for the esters and the corresponding acids are summarized in Table II.

Ring closure on an unsymmetrically substituted aniline, particularly a 3-substituted one, may give rise to isomeric 5- and 7-substituted quinolines. It is notable that in the case of 3-chloroaniline the product is almost exclusively the 7-chloro isomer.[7] Following this analogy the

TABLE I

CYCLIZATION OF SUBSTITUTED ANILINOMETHYLENEMALONIC ESTERS

Substituted methylenemalonic ester	M. p., °C.	Solvent	Dilution[c] cc./g.	Time, min.	3-Carbethoxy-4-quinolinols[d], %
Anilino-	49	D[a]	10	20	95.5
2-Nitroanilino-	101–102	D	10	20	80
2,2'-Dithio-bis-anilino-	Oil	D	40	20	4
3-Phenoxyanilino-	Oil	F[b]	10	30	45
4-Acetylanilino-	93–94	D	10	20	70
4-Chloroanilino-	82–83	D	10	20	80
4-Dimethylamino-anilino-	97–98	D	10	20	50
4-Nitroanilino-	142–143	D	20	20	90
4-Phenoxyanilino-	Oil	F	10	30	71
3,4-Dimethoxyanilino-	Oil	D	15	20	60
3-Chloro-4-benzylthioanilino-[e]	117–117.5	D	10	45	89
4,4'-Dithio-bis-(3-chloroanilino)-	90–100	D	10	20	71
4-Methoxy-2-nitroanilino-	126–127	D	10	20	85

[a] Dowtherm A, b. p. *ca.* 230–250°, a commercially available mixture of diphenyl ether and diphenyl. [b] Finol, a light mineral oil. [c] Volume of solvent in ml. per gram of anilino compound. [d] Based on the amount of the aniline used. [e] In the cyclization of this compound, a gel is formed which is most easily handled by direct saponification of the entire mass.

(1) The work described in this paper was done under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and Northwestern University.

(2) J. Meisenheimer, *Ber.*, **59**, 1848 (1926).

(3) A. C. Mueller and C. S. Hamilton, THIS JOURNAL, **65**, 1017 (1943).

(4) R. G. Gould and W. A. Jacobs, *ibid.*, **61**, 2890 (1939).

(5) C. C. Price, *ibid.*, **68**, 1204 (1946).

(6) L. Claisen, *Ann.*, **297**, 1 (1897), work cited on p. 77.

(7) Reported by C. C. Price at a conference of O.S.R.D. Contractors on the Synthesis of Antimalarial Drugs, Chicago, Ill., January 19, 1945.

TABLE II

3-CARBETHOXY-4-QUINOLINOLS AND 3-CARBOXY-4-QUINOLINOLS

Substituents	Ester M. p., °C.	Ester Formula	Ester Nitrogen, % Calcd.	Ester Nitrogen, % Found	Acid M. p., °C.[a]	Acid Formula	Acid Nitrogen, % Calcd.	Acid Nitrogen, % Found
None	269–270	$C_{12}H_{11}NO_3$	6.45	6.51	269	$C_{10}H_7NO_3$	7.40	7.47
8-Nitro-	252–253	$C_{12}H_{10}N_2O_5$	10.70	10.20	268	$C_{10}H_6N_2O_5$	11.96	11.61
8,8′-Dithio-bis-	260–262	Not analyzed			284	Not analyzed		
7-Phenoxy-	278–279	$C_{18}H_{15}NO_4$	4.53	4.36	269	$C_{16}H_{11}NO_4$	4.98	4.58
6-Acetyl-	298–300	$C_{14}H_{13}NO_4$	5.41	5.32	278	$C_{12}H_9NO_4$	6.08	6.23
6-Chloro-	>280	$C_{12}H_{10}NClO_3$	5.51	5.40	261	$C_{10}H_6ClNO_3$	6.27	6.29
6-Dimethylamino-	270–275 d.	$C_{14}H_{16}N_2O_3$	10.76	10.58	259	$C_{12}H_{12}N_2O_3$	12.08	11.68
6-Nitro-	>320	$C_{12}H_{10}N_2O_5$	10.70	10.02	>320	$C_{10}H_6N_2O_5$	11.96	11.60
6-Phenoxy-	274–275	$C_{18}H_{15}NO_4$	4.53	4.54	252	$C_{16}H_{11}NO_4$	4.93	4.88
6,7-Dimethoxy-	272–273	$C_{14}H_{15}NO_5$	5.06	5.01	276	$C_{12}H_{11}NO_5$	5.63	5.59
6-Benzylthio-7-chloro-	264–266	$C_{19}H_{16}ClNO_3S$	3.75	3.57	279	$C_{17}H_{12}ClNO_3S$	4.05	4.06
6,6′-Dithio-bis-(7-chloro)-	>300	$C_{24}H_{18}Cl_2N_2O_6S_2$	4.96	5.02	>300	$C_{20}H_{10}Cl_2N_2O_6S_2$	5.50	5.56
6-Methoxy-8-nitro-	222–224	$C_{13}H_{12}N_2O_6$	9.59	9.30	270	$C_{11}H_8N_2O_6$	10.61	10.75

[a] All of these compounds melt with decomposition.

TABLE III

4-QUINOLINOLS AND 4-CHLOROQUINOLINES

Substituents	Decarbox. method	4-Quinolinols Yield, %	M. p., °C.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	4-Chloroquinolines Yield, %	M. p., °C.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
None	1	95	214	C_9H_7NO	9.67	9.70	73.5	Oil	C_9H_6ClN	8.27	8.49
8-Nitro	2	0–30	198–199	$C_9H_6N_2O_4$	14.73	14.71	70	126–127	$C_9H_5ClN_2O_2$	13.43	12.74
7-Phenoxy-	1	70	183–184	$C_{15}H_{11}NO_2$	5.80	5.56	55	50–51	$C_{15}H_{10}ClNO$	5.50	5.10
6-Acetyl-	1	50	285–286	$C_{11}H_9NO_2$	7.49	7.15	20	47–48	$C_{11}H_8ClNO$	7.38	6.99
	2	90	285–286								
6-Chloro-	1	73	274–275	C_9H_6ClNO	7.78	7.67	85	105	$C_9H_5Cl_2N$	7.06	7.01
6-Dimethylamino-	2	85	265–269	$C_{11}H_{12}N_2O\cdot 2EtOH$[a]	10.00	10.33	60	225–230[b]	$C_{11}H_{11}ClN_2\cdot HCl$[b]	11.55	11.38
6-Phenoxy-	1	60	234–235	$C_{15}H_{11}NO_2$	5.80	5.93	71	50–51	$C_{15}H_{10}ClNO$	5.50	4.84
6,7-Dimethoxy-	2	50	236–237	$C_{11}H_{11}NO_2$	6.83	6.80	40	133–134	$C_{11}H_{10}ClNO_2$	6.27	6.41
6-Benzylthio-7-chloro-	2	80	208–209	$C_{16}H_{12}ClNOS$	4.64	4.74	90	136–137	$C_{16}H_{11}Cl_2NS$	4.38	4.42
6-Methoxy-8-nitro-	2	20	216–217	$C_{10}H_8N_2O_4$	12.71	12.51	75	187–188	$C_{10}H_7ClN_2O_3$	11.74	12.60

[a] The presence of alcohol of crystallization was proved by *semimicro Zerewitinoff* analysis; calcd. for three active hydrogens: 21.8 mg. of the dialcoholate requires 23.4×10^{-5} mole of methane. Found: 19.0×10^{-5} mole of methane. [b] This material was characterized as the hydrochloride. The free base is an oil.

7-position has been assigned to the phenoxy group in those quinolines made from 3-phenoxyaniline and to the chloro group in those quinolines derived from 3-chloro-4-benzylthioaniline and 4,4′-dithio-bis-(3-chloroaniline). It is probable that there is some steric hindrance to the closing of rings at positions adjacent to such large groups.

With the exception of 2,2′-dithio-bis-anilinomethylenemalonic ester, cyclization has given uniformly good yields. This compound was not extensively investigated since the ultimate aim was to prepare 4-chloro-8-quinolinesulfonyl chloride which, it was found, was very conveniently prepared through sulfonation of 4-chloroquinoline.[8]

The saponification of the resulting 3-carbethoxy-4-quinolinols to the corresponding acids is easy and gives quantitative yields. Some difficulty has been encountered in the decarboxylation of certain of the acids. This is particularly true of those acids containing nitro groups in the 8-position. Pyrolysis of these acids either in Dowtherm or by fusion gave yields of 0–50%. It was found that the heating of the silver salts in Dowtherm[9] gave uniformly better results[8] but, in the ultimate synthesis of 4-chloro-8-nitroquinoline, a direct nitration of 4-chloroquinoline has been preferred in this Laboratory.[8] It has not been possible to decarboxylate bis-(3-carboxy-4-hydroxy-7-chloro-6-quinolyl) disulfide by either of these methods. It appears essential that the acid be in the liquid state and in this case the melting point is so high and its solubility in Dowtherm so low as to preclude decarboxylation without general decomposition.

The decarboxylation of 3-carboxy-6,7-dimethoxy-4-quinolinol is successful only by fusion of the free acid. Even then there is occasionally formed a low-melting (120°) substance which, although it analyzes correctly, must not be 6,7-dimethoxy-4-quinolinol for it cannot be converted into the corresponding 4-chloro compound. The high melting substance usually obtained does not agree too well with that published by Lawson, Perkin and Robinson,[10] but since the melting point has been found to vary depending upon the method of drying, this discrepancy is judged to have little significance. This high melting compound is

(8) This will be described in a subsequent publication from this Laboratory.

(9) We are indebted to Prof. C. D. Hurd for suggesting this method.

(10) W. Lawson, W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.*, **125**, 626 (1924).

easily converted to the 4-chloro derivative. The analytical data and yields for the quinolinols and haloquinolines are summarized in Table III.

Acknowledgment.—We wish to thank Margaret Ledyard and Winifred Brandt for the microanalyses reported in this paper.

Experimental

Bis-(2-aminophenyl) Disulfide.—Bis-(2-nitrophenyl) disulfide was prepared from *o*-chloronitrobenzene and sodium disulfide[11] and this was reduced to the amine with hydrazine[12] in 56% yield.

3-Phenoxyaniline.—This was prepared by a modification of the method of Ullmann and Sponagel[13] in which *m*-chloroaniline was substituted for *m*-bromoaniline in the reaction with sodium phenoxide. The yield of 3-phenoxyaniline was 60% of the theoretical, b. p. 329–330°.

4-Phenoxyaniline.—4-Phenoxynitrobenzene[14] was reduced to the amine with zinc dust and calcium chloride[15] in 60% yield.

4-Aminoveratrole.—4-Nitroveratrole[16] was hydrogenated in ethanol solution using palladium on charcoal catalyst in the Adams reductor. The amine was not isolated and the ethanol solution was used directly after removing the catalyst by filtration.

4-Methoxy-2-nitroaniline.—A modification of the method of Reverdin[17] for the nitration of *p*-acetanisidide was used. To a mixture of 250 ml. of water and 250 ml. of concd. nitric acid at room temperature was added 50 g. (0.30 mole) of *p*-acetanisidide. The temperature rose to 45–50° and after two or three minutes a solid started to separate. The solution was then diluted with 500 ml. of cold water and the product collected by filtration. The yield of nearly pure 4-methoxy-2-nitroacetanilide, m. p. 115–116°, was 51 g. (82%). This was refluxed with 10 *N* sulfuric acid to give the amine, m. p. 125–126°.

4-Benzylthio-3-chloroaniline.—A solution of 63 g. (0.50 mole) of benzyl chloride, 38 g. (0.50 mole) of thiourea and three drops of concd. ammonium hydroxide in 250 ml. of ethanol was refluxed for three hours. To this was then added a solution of 96 g. (0.50 mole) of 3,4-dichloronitrobenzene in 200 ml. of ethanol and refluxing was continued while adding slowly a solution of 70 g. (1.25 moles) of potassium hydroxide in 500 ml. of ethanol. Refluxing was continued for two more hours, the mixture was cooled, and the product was collected by filtration. The yield of crude 4-benzylthio-3-chloronitrobenzene, m. p. 108–109°, was 113 g. (81%). This was reduced with tin and hydrochloric acid to give, in 83% yield, 4-benzylthio-3-chloroaniline m. p. 54–55.5°. Crystallized from 50% ethanol, the material melted at 56–57°.

Anal. Calcd. for $C_{13}H_{12}ClNS$: N, 5.61. Found: N, 5.44.

Bis-(4-amino-2-chlorophenyl) Disulfide.—The reaction of 3,4-dichloronitrobenzene with a freshly prepared solution of potassium disulfide using the method described for bis-(2-nitrophenyl) disulfide[18] gave in 80% yield bis-(3-chloro-4-nitrophenyl) disulfide, m. p. 126–129°. This was reduced with hydrazine by a modification of the method of Möhlau[12] in which a large excess of hydrazine was added during the course of the reduction which required twenty hours. The yield of bis-(4-amino-2-chlorophenyl) disulfide, m. p. 135–136°, was 95%. After crystallization from benzene the material melted at 146–147°.

Anal. Calcd. for $C_{12}H_{10}Cl_2N_2S_2$: N, 8.83. Found: N, 8.79.

Preparation of Anilinomethylenemalonic Esters.—Equimolar amounts of the aniline and ethoxymethylenemalonic ester were mixed and heated on the steam-bath until the evolution of ethanol had ceased. The time required for the nitroanilines was about twenty hours; for all others about two hours was sufficient. 4-Aminoveratrole was difficult to isolate and an alcoholic solution obtained by catalytic reduction of the nitro compound was used. This solution was added to the ethoxymethylenemalonic ester and heated until all the ethanol was removed. These compounds were not purified or characterized and were used immediately in the cyclization.

3-Carboxy-4-quinolinols.—Cyclization was effected by adding the melted anilinomethylenemalonic ester to the appropriate volume of refluxing Dowtherm A (see Table I) and refluxing until the evolution of ethanol ceased. In the case of the phenoxy substituted anilinomethylenemalonic esters, mineral oil preheated to 250° was used because of the high solubility of the products even in cold Dowtherm. The product separated on cooling and diluting the reaction mixture with two volumes of hexane. The product was collected by filtration, washed with hexane and acetone, and dried *in vacuo* at 100°. Most of the 3-carbethoxy-4-quinolinols could be recrystallized from ethanol or pyridine. The crude product was saponified by refluxing for two hours with excess 10% aqueous sodium hydroxide. Acidification with hydrochloric acid precipitated the 3-carboxy-4-quinolinol which was collected by filtration, washed with warm water and with acetone, and dried *in vacuo* at 100°. Saponification gave quantitative yields of the acids which could be recrystallized, in practically all cases, from ethanol or pyridine.

4-Quinolinols.—Two methods of decarboxylating the acids were used.

Method 1.—The dry powdered acid was heated at its melting point in a flask heated in a metal-bath or a heating mantle until the evolution of carbon dioxide had ceased. The crude quinolinol was dissolved in ethanol and the solution was treated with decoloring charcoal. The product obtained by evaporation of the ethanol could be further purified by a second crystallization.

Method 2.—The finely powdered acid was added to about five times its weight of refluxing Dowtherm and heating was continued until all the acid dissolved, usually about thirty minutes. The product precipitated on cooling and diluting with two volumes of hexane and was purified as before.

4-Chloroquinolines.—The 4-quinolinols were converted to 4-chloroquinolines by refluxing with excess phosphorus oxychloride for three hours. The excess phosphorus oxychloride was removed by distillation at steam-bath temperature and 20 mm. pressure and the residue was hydrolyzed with ice and water. The resulting solution was made alkaline with cold concd. ammonium hydroxide and the precipitate collected by filtration. The product was dissolved in boiling hexane and the solution decolorized by passing through a 5-cm. bed of powdered activated alumina. The 4-chloroquinolines crystallized on cooling.

Summary

1. The formation and cyclization of various anilinomethylenemalonic esters gave substituted 3-carbethoxy-4-quinolinols.

2. The 3-carbethoxyl group was removed by hydrolysis and decarboxylation.

3. The resulting 4-quinolinols were converted into the corresponding 4-chloroquinolines.

4. Other methods for the preparation of 4-chloroquinolines containing substituents in the carbocyclic ring are discussed.

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