Summary

1. Improved procedures for the preparation of α-alkylphenylacetonitriles and γ-chloro-α-alkyl-α-phenylbutyronitriles have been developed.

2. Four new pyrrolines have been prepared by the action of phenylmagnesium bromide on the γ-chloro-α-alkyl-α-phenylbutyronitriles. The alkyl substituents used were methyl, ethyl, *n*-propyl and *n*-butyl. The chloroplatinates and picrates derived from the pyrrolines have been reported.

3. The method of synthesis of these pyrrolines points to the Δ^1 structure. The free pyrrolines resinify upon standing, a property which has been attributed to the Δ^2-pyrrolines by some writers.

TROY, N. Y. RECEIVED SEPTEMBER 28, 1945

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF WINTHROP CHEMICAL COMPANY, INC.]

Quinolines. I. The Synthesis of 3-Methyl-4-(1'-methyl-4'-diethylaminobutylamino)-quinoline and Some 6-Substituted Derivatives

BY EDGAR A. STECK, LOUIS L. HALLOCK AND ARNOLD J. HOLLAND[1]

There has been considerable interest in 6-substituted quinolines because of the importance of the 6-methoxy group in the activity of quinine and pamaquin.[1a] The investigation of various 6-substituted quinolines has been of considerable scope since the synthesis of pamaquin, and many modifications of the nucleus and side-chain have been studied in attempts to increase the activity and lower the toxicity. Despite the great amount of information on 6-substituted quinolines having a basic chain attached to the 8-position, the study of the corresponding 4-dialkylaminoalkylamino types has received rather little attention.[2-10] The findings of the Russian investigators[2,3] have indicated clearly that the curative properties of the nucleus are not destroyed when the side-chain is attached at position 4, and also have shown that the compounds of this type no longer possess the gametocidal or gametostatic action of pamaquin, but, rather, a schizontocidal action in the manner of quinine and quinacrine. This latter observation apparently led to the interest of Gilman and Spatz[8] in the quinoline compounds which may be considered as "open models" of quinacrine, *viz.*, 6-methoxy-2-(3'-chlorophenyl)-4-(1'-methyl-4'-diethylaminobutylamino)-quinoline and related types.

Despite the indications of the work of Strukov,[2,3] Holcomb and Hamilton[7] and Van Arendonk and Shonle[9] have shown interest in 4-substituted 2-methylquinolines. The unpublished work of Strukov (1932) referred to by Magidson and by Gal'perin was upon three 2-methyl-6-methoxyquinolines having dialkylaminoalkylamino groups in position 4: *viz.*, the 4-diethylaminobutylamino, the 3-diethylamino-2-hydroxypropylamino and the 3-diethylaminopropylamino side-chains. There is essentially no information concerning the activity of analogous compounds having the methyl group in position 3, other than two patents,[4,5] which have been issued on certain compounds having a substituent in that position. The patents state that the compounds are effective against blood parasites, particularly plasmodia. The present contribution represents the first of a series dealing with the synthesis of 4-dialkylaminoalkylaminoquinolines carrying an alkyl group in position 3 and one or more substituents in the benzene ring. The compounds herein reported are all 3-methyl-4-(1'-methyl-4'-diethylaminobutylamino)-quinolines with hydrogen or a substituent (chloro, bromo, methoxy, ethoxy, or methyl) in position 6.

The method employed in the synthesis of the desired compounds is based upon the procedure of Conrad and Limpach[11,12] for the formation of 4-hydroxyquinoline derivatives from anilines and β-keto esters. Indication of the use of ethyl ethoxalylpropionate in the preparation of the 3-R (where R is CH_3) quinolines is given in the patents[4,5] mentioned above. No details are given for the procedure in either of the patents, hence it will be discussed in detail. As indicated by the equations, the aniline (I) and ethyl ethoxalylpropionate (II) are caused to react, and the product (III) is then readily cyclized at 250–260° to the quinoline ester, IV. The yields in both reactions are good, the first being 80% or better, and in the second the yields exceed 90%. Hydrolysis of the ester, IV, by aqueous sodium hydroxide, leads to nearly quantitative yields of the corresponding acid, V. The decarboxylation of V is most effectively carried out in mineral

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(2) Magidson and Rubtsov, *J. Gen. Chem.* (*U. S. S. R.*), **7**, 1896 (1937).

(3) Gal'perin, *Med. Parasitol. Parasitic Diseases* (*USSR*), **9**, No. 1-2, 44 (1940).

(4) Andersag, Breitner and Jung, U. S. Patent 2,233,970; *C. A.*, **35**, 3771[7] (1941).

(5) Andersag, Breitner and Jung, German Patent 683,692; *C. A.*, **36**, 4973[8] (1942).

(6) Schönhöfer, *Z. physiol. Chem.*, **274**, 1 (1942).

(7) Holcomb and Hamilton, THIS JOURNAL, **64**, 1310 (1942).

(8) Gilman and Spatz, *ibid.*, **66**, 621 (1944).

(9) Van Arendonk and Shonle, *ibid.*, **66**, 1284 (1944).

(10) Schulemann, Schönhöfer and Wingler, U. S. Patent 1,747,531; *C. A.*, **24**, 1705[9] (1930).

(11) Conrad and Limpach, *Ber.*, **20**, 944 (1887).

(12) Limpach, *ibid.*, **64**, 969 (1931).

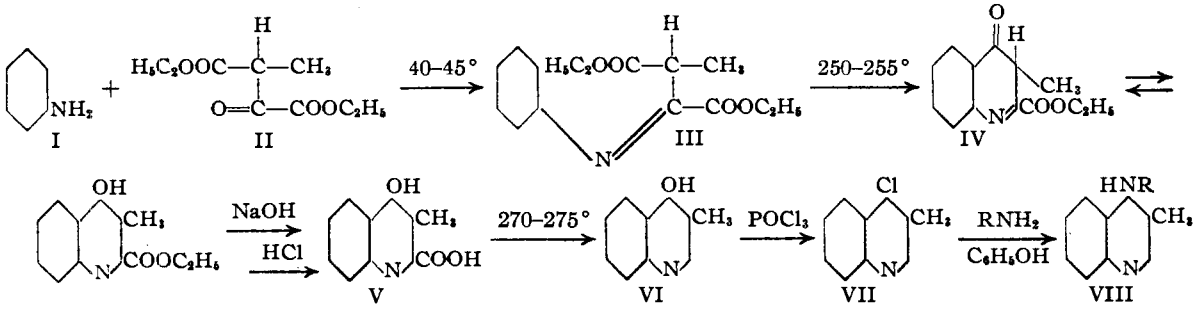
TABLE I

3-METHYLQUINOLINE DERIVATIVES

Compound	Yield[a] %	Appearance	Solvent[f]	M. p.,[b] °C.	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Ethyl 3-Methyl-4-hydroxyquinoline-2-carboxylates										
Unsubstituted	85	Fine white needles	aE	178	67.52	5.67	6.06	68.02	5.76	6.43
6-Chloro	95	White needles	E	251	58.76	4.55	5.27	58.65	4.26	5.79
6-Bromo	77	White platelets	E	251	50.34	3.90	4.52	50.37	4.11	4.89
6-Methoxy	97	White needles	E	186	64.35	5.78	5.37	64.49	6.16	5.80
6-Ethoxy	95	White needles	E	194	65.44	6.23	5.09	65.88	6.50	5.56
6-Methyl	92	White needles	aAc	183	68.55	6.17	5.71	68.75	6.49	5.86
3-Methyl-4-hydroxyquinoline-2-carboxylic Acids										
Unsubstituted	90	Creamy-white microc.	P	300	65.02	4.47	6.89	65.12	4.85	7.05
6-Chloro	95	Pale yell. microcryst.	aA	d265	55.59	3.47	5.89	55.76	3.53	6.04
6-Bromo	100	White needles	aE	d257	46.83	2.86	4.97	[c]	[c]	4.75
6-Methoxy	100	Pale yell. microcryst.	P	d263	61.80	4.75	6.01	62.05	5.06	6.10
6-Ethoxy	90	White microneedles	P	d249	63.15	5.30	5.67	[c]	[c]	5.71
6-Methyl	100	White microcryst.	P	d252	66.25	5.10	6.45	66.17	5.60	6.85
3-Methyl-4-hydroxyquinolines										
Unsubstituted	92	White needles	aAc	231	75.50	5.70	8.81	75.39	5.54	8.73
6-Chloro	92	White needles	E	>300	62.02	4.17	7.24	62.01	4.52	7.23
6-Bromo	95	Creamy white needles	aE	>300	50.44	3.39	5.88	50.65	3.59	5.63
6-Methoxy	86	Creamy white microcryst.	E	257	69.82	5.86	7.40	69.77	5.73	7.30
6-Ethoxy	88	Fine white needles	E	244	70.92	6.45	6.89	71.59	6.75	6.77
6-Methyl	94	Pale yell. needles	aE	245	76.27	6.40	8.09	76.71	6.76	8.45
3-Methyl-4-chloroquinolines										
Unsubstituted	95	Fine white needles	S[d]	60	67.61	4.54	7.89	67.57	4.82	7.71
6-Chloro	90	White needles	E	116	56.87	3.34	6.63	56.97	3.74	7.03
6-Bromo	95	White needles	aE	144	46.81	2.75	5.46	47.39	3.11	5.55
6-Methoxy	92	Creamy white needles	aM	88	63.48	6.11	6.78	63.58	5.82	6.68
6-Ethoxy	89	White needles	aM	72	65.01	5.46	6.32	64.96	4.98	6.47
6-Methyl	92	White needles	aE	58	68.94	5.26	7.31	68.70	5.51	7.45
3-Methyl-4-(1'-methyl-4'-diethylaminobutylaminoquinolines)				B. p., °C.	Mm.					
Unsubstituted	83	Lemon-yellow oil		180	0.5	76.20	9.77	14.03	76.03	9.67	13.89
6-Chloro	87	Golden yellow oil		190	.8	68.40	8.46	12.62	68.85	8.12	13.07
6-Bromo	87	Golden yellow oil[e]		196	.8	60.31	7.46	11.11	59.94	7.85	11.46
6-Methoxy	61	Golden yellow oil[e]		186	.6	72.90	9.56	12.75	72.75	9.85	12.58
6-Ethoxy	61	Bright yellow oil		190	.4	43.43	9.68	12.23	73.80	9.45	12.55
6-Methyl	80	Pale yell. oil[e]		177	.5	76.63	9.97	13.70	76.60	9.91	13.47

[a] Not purified—as used for next stage. [b] Corrected; d = decomposes. [c] C and H analyses not concordant. [d] Very soluble, sublimed. [e] Solidified very slowly, but could not be crystallized. [f] Legend: A, acetic acid; Ac, acetone; E, ethanol; M, methanol; P, propylene glycol; a, aqueous (usually 20% water).

oil at 270–275°, the yields exceeding 90%. Replacement of the hydroxyl group in the compound (VI) so formed is accomplished by boiling with phosphorus oxychloride; excellent yields (90–95%) of the 4-chloro compound (VII) result. The basic side-chain is attached to position 4 by the reaction of the chloro compound (VII) with the requisite dialkylaminoalkylamine in phenol,



preferably in the presence of a small amount of sodium iodide as catalyst.[4] The yields of the 3-methyl-4-dialkylaminoalkylaminoquinoline (VIII) are 65–85% when the final reaction temperature is maintained at 165–175°; considerably lower yields result when the temperature is permitted to vary from the range specified.

Experimental

Anilines.—All *p*-substituted anilines employed were purified until the constants were essentially those recorded in the literature.

Ethyl Ethoxalylpropionate.[13]—The preparation of this ketoester was effected by the condensation of ethyl oxalate (1100 g., 7.55 moles) with ethyl propionate (1500 g., 1.47 moles) in the presence of 95% sodium methoxide (900 g.) in dry benzene (3 liters), and the reaction mixture was refluxed for two hours, with stirring. It was allowed to stand four hours, then poured into a well-stirred mixture of 12 liters of water and 1100 ml. of glacial acetic acid. After stirring for two hours, the benzene layer was separated, the aqueous layer extracted with ether, and the extracts combined and dried over anhydrous sodium sulfate. The solvents were removed and the residual liquid fractionated to yield 955–1190 g. (46–57%) of ethyl ethoxalylpropionate, b. p. 75–78° (2 mm.), $n^{20}D$ 1.4313.

Ethyl 3-Methyl-4-hydroxyquinoline-2-carboxylates.—An equimolecular mixture of the appropriate aromatic amine and ethyl ethoxalylpropionate was heated at 40–45° for twenty-four to forty-eight hours in methylene chloride solution, using 50 ml. of solvent for each tenth-molar reaction mixture, and the amount of water eliminated measured in a water-separator. Any excess amine present was removed from the methylene chloride solution by extraction with several portions of 0.5 *N* hydrochloric acid, then the organic layer was dried over anhydrous sodium sulfate after washing with water, 0.5 *N* sodium hydroxide; and again with water to ensure removal of all acid. It was also found possible to carry out these reactions with essentially the same yields as when methylene chloride was used, by employing no solvent or glacial acetic acid (*ca.* 50 ml. per 0.1 mole of reagents) as the solvent. In the former case, the reaction mixture was merely mixed with methylene chloride and worked up as when that solvent was used. If acetic acid were the solvent, however, the solution was poured onto ice and basified with 35% aqueous sodium hydroxide, then extracted with methylene chloride, followed by the usual procedure for removal of amine. The solvent was removed and any traces of ester present were removed by distillation *in vacuo*. The crude condensation products (III) so obtained in yields of 78–95% (direct, not upon the basis of unrecovered amine) were malodorous orange to brown oils. As usual, these compounds were cyclized directly, without purification.

Cyclization was effected by the gradual addition of the crude starting material (III) to medicinal grade mineral oil (5–8 ml. per g. condensate) stirred vigorously at 250–255° in a three-necked flask equipped with dropping funnel, stirrer and condenser set for distillation. When approximately the theoretical quantity of alcohol had been collected (this required five to ten minutes of heating at 250–255° after the azomethine had been added), the oil was allowed to cool while stirring. The oil was removed from the quinoline ester (IV) by thorough washing with Skellysolve A; a few of these compounds were somewhat soluble in the Skellysolves. It was found that the crude esters were quite satisfactory for the remainder of the synthesis.

3-Methyl-4-hydroxyquinoline-2-carboxylic Acids.—Hydrolysis of the esters (IV) to the acids (V) was accomplished by refluxing with three moles of sodium hydroxide (as a 5% aqueous solution) for two and one-half to three hours. The resulting solution was treated with Darco S-51, then the acid precipitated by the addition of 1:1 hydrochloric acid and washed thoroughly with water, then dried to constant weight. It was found expedient to employ purified samples of ester when analytically pure samples of acid were desired, for otherwise the product was not readily purified.

3-Methyl-4-hydroxyquinolines.—The crude, finely powdered quinoline acid, V, was most effectively decarboxylated by adding it gradually to medicinal grade mineral oil (*ca.* 10 ml. per g. of acid) stirred well at 270–275°. It was frequently necessary to maintain the oil at a temperature of 270–280° for a few minutes after the addition of the acid, for otherwise there was incomplete decarboxylation. The mixture was stirred while cooling and then the oil removed from the resulting crystals with the acid of Skellysolve A.

3-Methyl-4-chloroquinolines.—The crude decarboxylated material (VI) was refluxed with a large excess of phosphorus oxychloride (*ca.* 5 ml. per g. of VI) until no more hydrogen chloride was evolved; this usually required about three hours. This converts the 4-hydroxy group into the 4-chloro group (VII). After removal of the greater portion of the excess phosphorus oxychloride by distillation under reduced pressure, the residues were decomposed by gradually adding to ice, then basifying with concentrated ammonium hydroxide. The greater portion of the product (VII), usually a low-melting solid, was obtained directly, but the mother liquors frequently yielded a considerable amount when extracted with methylene chloride, dried over anhydrous sodium sulfate, and the solvent removed. All solids obtained were thoroughly washed with ice water to remove salts, then dried thoroughly.

3-Methyl-4-dialkylaminoalkylaminoquinolines.—A mixture of the chloro compound (VII) and one and one-half times its weight of phenol was melted and stirred at 100°, then a small amount of powdered sodium iodide (*ca.* 50 mg. for 50–75 g. of chloro compound) was added. After heating at 100–125° for five to ten minutes, the requisite side-chain amine (here 1-methyl-4-diethylaminobutylamine was used) was introduced, employing approximately 100% excess. The temperature of the well-stirred mixture was raised gradually by heating in an oil-bath. In some cases the vigor of the reaction may cause the internal temperature to rise as much as 40° above that of the bath if care is not exercised; poor yields result when this occurs. The internal temperature of the reaction mixture is maintained at 165–175° until complete. The completion of the reaction was ascertained by the following test (*cf.* ref. 4). A few drops of the reaction mixture was dissolved in 2–3 ml. of 2 *N* nitric acid and about three times its volume of saturated aqueous sodium acetate solution added. If there was only a slight cloudiness, the reaction was considered complete. It was found that most of the reactions of this type require ten or more hours at 165–175° for completion.

The viscous, brownish oil obtained at the end of the heating period was mixed well with a large excess of 35% aqueous sodium hydroxide solution and extracted with ether or methylene chloride. To remove the bases, the extracts were treated, in one portion, with a slight excess of 2 *N* hydrochloric acid, so that the aqueous layer gave an acid reaction with congo red. The aqueous layer was separated and stirred with ether or methylene chloride, then impurities were removed by addition of solid sodium acetate until the mixture was neutral to congo red. The layers were separated and then the aqueous phase was extracted once with the same solvent as previously employed and the extracts rejected. After covering with ether (methylene chloride may be used), the acidic aqueous portion was stirred well during the addition of 35% aqueous sodium hydroxide solution until the *p*H was 9–10. The organic layer was separated and the liquors further extracted, then all extracts combined and dried over anhydrous potassium carbonate. The solvent was removed and the excess side-chain amine distilled off under reduced pressure (less than 4 mm.). The viscous residual oil consisted chiefly of the desired 3-methyl-4-dialkylaminoalkyl-

(13) *Cf.* Cox and McElvain, "Organic Syntheses," Coll. Vol. II 1943, p. 272.

aminoquinoline, VIII. It was found necessary to distill these compounds very slowly, and in small amounts, at pressures of less than 1 mm. from a modified Claisen flask, otherwise decomposition occurred readily.

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Summary

A series of 6-substituted 3-methyl-4-(1′methyl-4′-diethyl-aminobutylamino)-quinolines has been prepared and is described, together with the intermediates.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF WINTHROP CHEMICAL COMPANY, INC.]

Quinolines. II. The Synthesis of 8-Substituted 3-Methyl-4-(1′-methyl-4′-diethyl-aminobutylamino)-quinolines

BY EDGAR A. STECK, LOUIS L. HALLOCK AND ARNOLD J. HOLLAND[1]

The present contribution represents a continuation of the study[1a] of benzene-substituted 4-dialkylaminoalkylaminoquinolines bearing a substituent in position 3. Initiation of the program of study of these compounds was due to an interest in the development of drugs for combatting certain parasites which infect the blood stream. The compounds which have been synthesized in this phase of the investigation have the 8-position substituted by one of the same groups as reported in the first paper,[1a] *viz.*, chloro, bromo, methoxy, ethoxy and methyl. It is of interest to note that the use as pharmaceuticals of such derivatives of the quinoline series was considered in a patent issued as early as 1930.[2]

As in the previous work, the desired quinolines were prepared by the application of the synthesis of Conrad and Limpach[3,4] by means of which 4-hydroxyquinolines may be prepared from anilines and β-keto esters. The compounds required for this portion of the extended study of quinoline derivatives were prepared by the use of *o*-substituted anilines and ethyl ethoxalylpropionate as starting materials. A detailed description has been given[1a] of the scheme employed in the synthesis, hence only an outline is presented here. The aniline and β-keto ester were condensed to yield an azomethine, which was then cyclized at 250° to give an 8-substituted ethyl 3-methyl-4-hydroxyquinoline-2-carboxylate. Hydrolysis of the ester with aqueous alkali led to the carboxylic acid, which decarboxylated readily at 270° to produce an 8-substituted 3-methyl-4-hydroxyquinoline. The reaction of the hydroxy compound with boiling phosphorus oxychloride gave the corresponding chloroquinoline, which was converted into the desired 8-substituted 3-methyl-4-(1′-methyl-4′-diethylaminobutylamino)-quinoline by reaction with 1-methyl-4-diethylaminobutylamine in phenol. In several instances differences were noted in the behavior of the compounds involved in the present synthesis, as compared with that observed in the 6-substituted series. The condensation reaction of the *o*-substituted anilines to the azomethines gave considerably poorer yields of product, and correspondingly larger amounts of the anilines were recovered. It appears to be possible that the lesser degree of reactivity of the *o*-substituted anilines was due to either the lower basicity of the amines,[5,6] or to steric effects. The lower yields of esters obtained upon cyclizing the azomethines were found to be due to the solubility of these compounds in the Skellysolve employed in the removal of the mineral oil employed in the cyclizations. In the subsequent steps, the results were as satisfactory as the corresponding ones in the 6-substituted series of quinolines.

Experimental

Anilines.—All of the *o*-substituted anilines employed were commercial samples purified until the physical constants agreed essentially with those reported in the literature.

Ethyl Ethoxalylpropionate.—The preparation of this ester was carried out as described previously.[1a]

Ethyl 3-Methyl-4-hydroxyquinoline-2-carboxylates.—The condensations of the appropriate *o*-substituted anilines with ethyl ethoxalylpropionate were carried out in methylene chloride, or acetic acid, or without solvent, after the manner of the procedure outlined in the first paper.[1a] The yields of crude azomethines obtained varied from 62 to 88%; the recovery of unreacted amine from the hydrochloric acid washings amounted to 10–24% of that employed.

The crude, brownish azomethines were cyclized in the

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(1a) First paper: Steck, Hallock and Holland, THIS JOURNAL, **68**, 129 (1946).

(2) Schulemann, Schönhöfer and Wingler, U. S. Patent 1,747,531; *C. A.*, **24**, 1705 (1930).

(3) Conrad and Limpach, *Ber.*, **20**, 944 (1887).

(4) Limpach, *ibid.*, **64**, 969 (1931).

(5) Farmer and Warth, *J. Chem. Soc.*, **85**, 1713 (1904).

(6) Hall and Sprinkle, THIS JOURNAL, **54**, 3469 (1932).