TABLE II

"d" VALUES OF SUBSTITUTED 8-QUINOLINOLS (IN ORDER OF DECREASING INTENSITY)

Substituent								
None	6.27	3.18	3.82	3.50				
5,7-Br_2-	3.52	3.89	4.06	4.26	3.09	3.20	3.36	6.81
2-CH_3-	3.92	3.67	3.13	5.45	5.93	2.07	5.00	7.94
5,7-Br_2-2-CH_3-	3.52	4.64	3.78	3.10				
4-CH_3-	3.30	6.01	7.29					
2,4-$(CH_3)_2$-	7.14	3.55	3.98	4.50	3.24			
5,7-Br_2-2,4-$(CH_3)_2$-	4.03	3.42	4.31					

same properties with the important exception that 2-methyl- and 2,4-dimethyl-8-quinolinol will not form insoluble chelate compounds with aluminum, the smallest ion of the group tested. Since 4-methyl-8-quinolinol will precipitate aluminum, it seems probable that the 2-methyl group prevents reaction with aluminum by steric hindrance. Further evidence of steric effects by the 2-methyl group is the observation that 2-methyl- and 2,4-dimethyl-8-quinolinol do not give the red addition products with diazomethane that are obtained from 8-quinolinol and 4-methyl-8-quinolinol under comparable conditions.

Quantitative data on the precipitation behavior of these compounds with metals are presented in Table III; the similar results for 8-quinolinol as determined by Goto[11] are included for comparison.

TABLE III

THE *p*H OF PRECIPITATION OF METAL CHELATES OF SUBSTITUTED 8-QUINOLINOLS

Substituent ion	None[d] Start[a]	None[d] End[b]	4-CH_3 Start	4-CH_3 End	2-CH_3 Start	2-CH_3 End	2,4-$(CH_3)_2$ Start	2,4-$(CH_3)_2$ End
Al^{+3}	2.8	4.2	3.5	...	None	None	None	None
Fe^{+3}	2.4	2.8	2.4	3.6	3.1[c]	5.7[c]	3.0	5.4
Mg^{+2}	6.7	8.2	6.8	8.4	7.6[c]	8.9[c]	8.2	>9.5
Mn^{+2}	4.3	5.9	4.6	6.0	5.0	6.6	5.2	7.0
Co^{+2}	2.8	4.2	3.4	4.6	3.8	5.2	4.2	5.8
Zn^{+2}	2.8	4.4	3.2	5.2	3.4[c]	5.3[c]	3.2	5.2
Cd^{+2}	2.2	2.7	...	3.4	2.9[c]	4.5[c]	2.4	4.8

[a] The highest *p*H without any precipitation. [b] The lowest *p*H at which the metal is wholly precipitated. [c] Previously determined.[2] [d] Previously determined.[11]

It is interesting that the order of increasing *p*H at which a given metal ion is precipitated by these four compounds is roughly the order of decreasing acidity of the substituted 8-quinolinols (the ionization constants have been previously reported[3]).

8-Quinolinol
4-Methyl-8-quinolinol
2-Methyl-8-quinolinol
2,4-Dimethyl-8-quinolinol

increasing K_a ↑ ↓ increasing *p*H

This is explained by noting that, although the weaker acids should form more stable complexes with metallic ions[12] and should, therefore, form precipitates in more acid solutions, it is necessary to go to more basic solutions in order to obtain comparable amounts of the active chelating ion. The latter effect is apparently the predominant one.

Summary

1. The ultraviolet and infrared absorption spectra of the 2- and 4-methyl derivatives of 8-quinolinol have been measured and their correlation with structure discussed.

2. The precipitation behavior of these compounds with metal ions has been determined and evidence for steric hindrance by the 2-methyl group in such reactions presented.

3. The possible relation of the function of the acidic hydrogen in 8-quinolinol to that of the metal ion in the corresponding chelate, as shown by the relation of K_a to *p*H of precipitation, has been pointed out.

(11) H. Goto, *J. Chem. Soc. Japan*, **54**, 725 (1933), and later references.

(12) Calvin and Wilson, THIS JOURNAL, **67**, 2003 (1945).

BLOOMINGTON, IND. RECEIVED APRIL 25, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, INDIANA UNIVERSITY]

Preparation of Some Substituted 8-Hydroxy- and 8-Methoxyquinolines

BY JOHN P. PHILLIPS,[1] REBECCA LEASH ELBINGER[1,2] AND LYNNE L. MERRITT, JR.

As a result of the discovery[3] that 8-hydroxyquinaldine differed in its analytical behavior from 8-hydroxyquinoline, the compounds here described were synthesized with the hope of obtaining more selective analytical reagents of the 8-hydroxyquinoline series.

The steric nature of the failure of 8-hydroxyquinaldine to react with aluminum was demonstrated by the observation that all the 8-quinolinols studied having alkyl groups in the 2-position would not react with aluminum while the isomeric compounds with substituents in the 3- and 4-positions would react. With the expectation that larger groups in the 2-position would create greater steric hindrance, perhaps enough to prevent reaction with other metal ions besides aluminum, a series of 2-aryl- and 2-styryl 8-quinolinols was prepared, but qualitative tests with several representative metal ions indicated no improvement in selectivity.

All alkyl substituted 8-hydroxy- and 8-methoxyquinolines (Table I) were made by the Doebner–

(1) Abstracted in part from theses submitted by Rebecca Leash Elbinger and John P. Phillips in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Indiana University.

(2) Present address: University of Illinois Extension, Navy Pier, Chicago, Illinois.

(3) L. L. Merritt and J. Walker, *Ind. Eng. Chem., Anal. Ed.*, **16**, 387 (1944).

von Miller reaction[4] between α,β-unsaturated carbonyl compounds and *o*-aminophenol or *o*-anisidine. No effective oxidizing agent for these reactions was found. (Nitrobenzene, *o*-nitrophenol and picric acid were tried.) This probably accounts, in part, for the very low yields obtained.

The 2-aryl-8-quinolinols (Table I) were prepared by the reaction of an excess of the proper lithium aryl with 8-quinolinol according to the method of Gilman.[5] The preparation of the corresponding 8-methoxy derivatives from 8-methoxyquinoline could be effected with greater economy of the lithium aryl, but it was not found possible to cleave the resulting ethers by the usual procedures at ordinary pressures using hydriodic acid, hydrobromic acid or potassium hydroxide and ethylene glycol.

2-Styryl-8-quinolinol and some related compounds (Table I) were made by the condensation, by heating, of 8-hydroxyquinaldine with benzaldehydes.

TABLE I

SUBSTITUTED 8-QUINOLINOLS AND 8-METHOXYQUINOLINES

Substituent	M. p. (uncor.), °C.	Yield, %	Nitrogen, % Calcd.	Nitrogen, % Found	Procedure
8-Quinolinols					
4-CH_3– [a]	141	20	8.80	9.01	A
2,4-$(CH_3)_2$– [b]	64	32	..	..	A
2,4-$(CH_3)_2$-5,7-Br_2–	108	100	.. [c]	..	.. [d]
3,4-$(CH_3)_2$–	123–124	5	8.14	8.51	A
2,3,4-$(CH_3)_3$–	89–91	5	6.96	6.83	A
2-C_2H_4-3-CH_3–	46–47	5	.. [e]	..	A
2-C_2H_5-3-CH_3-5,7-Br_2–	150	100	4.06	4.29	.. [d]
2-C_6H_5– [f]	59	44	6.34	6.27	B
2-*m*-$CH_3C_6H_4$–	58–59	30	5.96	5.83	B
2-*p*-$CH_3C_6H_4$–	83–83.5	32	5.96	6.10	B
2-*p*-$C_6H_5C_6H_4$–	170–171	30	4.71	4.71	B
2-*p*-$CH_3OC_6H_4$–	101–102	30	5.58	5.52	B
2-*p*-$C_2H_5OC_6H_4$–	84–85	30	5.29	5.15	B
2-*p*-$(CH_3)_2NC_6H_4$– [g]	151–152	30	10.6	10.7	B
2-*p*-$(C_2H_5)_2NC_6H_4$–	94–95	34	9.60	9.98	B
2-C_6H_5CH=CH–	104–105	50	5.66	5.47	C
2-*m*-$CH_3C_6H_4CH$=CH–	60–61	36	5.36	5.47	C
2-*p*-$CH_3OC_6H_4CH$=CH–	110–111	30	5.05	5.10	C
2-(2,3-$(CH_3O)_2$)-C_6H_4CH=CH–	102–103	30	4.56	4.43	C
8-Methoxyquinolines					
2,4-$(CH_3)_2$–	99–100	...	7.48	7.72	A
2,3,4-$(CH_3)_3$–	99–102	...	7.00	6.68	A
2-C_6H_5–	69.5–70.5	70	5.96	6.04	B
2-*o*-$CH_3C_6H_4$–	171	28	5.62	5.62	B
2-*m*-$CH_3C_6H_4$–	86–87	40	5.62	5.18	B
2-*p*-$CH_3C_6H_4$–	94–94.5	53	5.62	5.76	B

[a] This compound previously prepared by a different method.[6] [b] Previously prepared in unspecified yield by this reaction, recorded m. p. 64°.[7] [c] Analysis for Br: Calcd.: 48.28; found: 47.98. [d] Prepared by quantitative bromination of the parent compound with std. potassium bromate. [e] Analysis of copper salt for Cu: Calcd.: 14.7; found: 14.5. [f] Previously prepared by a different method.[8] [g] Previously made in unspecified yield by this reaction.[4]

(4) O. Doebner and W. von Miller, *Ber.*, **16**, 1665, 2465 (1883).

(5) H. Gilman, J. Towle and S. Spatz, THIS JOURNAL, **68**, 2017 (1946).

(6) Busch and Koenigs, *Ber.*, **23**, 2686 (1890).

(7) Bauer and Engler, *ibid.*, **22**, 210 (1889).

(8) O. Doebner and Fettback, *Ann.*, **281**, 9 (1894).

Most of the 8-quinolinols prepared showed little or no fluorescence under ultraviolet light, while the corresponding 8-methoxy compounds generally had a strong blue-white fluorescence.

Data on the ultraviolet and infrared absorption spectra, X-ray powder diffraction patterns and quantitative reactions with metal ions of these compounds will be reported later.

Experimental

A. The general procedure used to make the alkyl substituted 8-quinolinols was as follows:

One-quarter of a mole (27.3 g.) of *o*-aminophenol was added to 100 ml. of concentrated hydrochloric acid in a flask fitted with condenser, stirrer and dropping funnel. The flask was heated to about 100° and a 30–100% excess of the appropriate α,β-unsaturated carbonyl compound added dropwise over a period of thirty to forty-five minutes. After stirring for six hours at 100–120°, the mixture was allowed to stand overnight and then steam distilled briefly to remove volatile impurities. It was then made slightly alkaline to litmus and steam distilled until all the product had come over. The products were recrystallized from alcohol–water mixtures.

The procedure used to make the 8-methoxyquinolines from *o*-anisidine differed from the above in that, after making the solution alkaline to litmus with sodium hydroxide, a gummy solid separated which was distilled under reduced pressure to obtain the product. The 8-methoxyquinolines were recrystallized from petroleum ether or cyclohexane.

In several cases it was possible to prepare the equivalent of the α,β-unsaturated carbonyl compounds by saturating a mixture of the aldehyde and ketone which were to be condensed with dry hydrogen chloride and using the resulting chloroketone without isolation, as suggested by Bauer and Engler.[7] This procedure naturally gave lower yields than when the intermediate unsaturated carbonyl compounds were isolated before use, as was usually done. Aldol condensation type reactions recorded in the literature were used to make these compounds.

B. The general method for making the 2-aryl-8-quinolinols was the following:

In a three-necked flask fitted with stirrer, dropping funnel, and condenser protected from moisture, the whole system being swept with dry nitrogen, were placed 300 ml. of dry ether and 3.5 g. (0.5 mole) of lithium metal cut into thin shavings. One quarter of a mole of the required aryl bromide was added dropwise, a vigorous reaction occurring. After the reaction was over, 0.05 mole (7.3 g.) of 8-quinolinol dissolved in ether was added over five to ten minutes. Stirring was continued for forty-five minutes and the mixture was then poured over ice and the ether layer separated. After removal of the ether by distillation, the residue was dissolved in hot dilute hydrochloric acid and then neutralized with sodium carbonate. An oil (or sometimes a solid) separated which was distilled under reduced pressure. The products generally boiled between 240 and 320° at approximately 25 mm. They were recrystallized from 95% alcohol.

The corresponding 8-methoxy compounds were prepared similarly from 8-methoxyquinoline except that, after removing the ether, vacuum distillation gave the desired products directly. These were recrystallized from petroleum ether.

The use of nitrogen was later found to be an unnecessary precaution since refluxing ether served to keep air out of the reaction flask.

C. The condensation of 8-hydroxyquinaldine or 8-methoxyquinaldine with aromatic aldehydes was effected by this general procedure:

One-tenth of a mole (15.9 g.) of 8-hydroxyquinaldine was refluxed with 30–40 g. of the required aldehyde if it boiled below 180° or heated at 150–175° if the aldehyde was high boiling, for five hours. The mixture was then

vacuum distilled to obtain the products, which were all light yellow solids. These compounds were recrystallized from 95% alcohol.

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Summary

Several new 8-quinolinols substituted in the pyridine ring have been prepared. Several new substituted 8-methoxyquinolines have also been prepared. The steric hindrance of substitution of 8-quinolinol in the 2-position on the reaction with aluminum ion is shown by the fact that shifting the substituent to the 3- or 4-position permits reaction.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Antispasmodics. II. Tertiary Aminoalkane Thiol Esters of Disubstituted Acetic Acids

BY H. G. KOLLOFF, JAMES H. HUNTER, E. H. WOODRUFF AND ROBERT BRUCE MOFFETT

Studies of synthetic spasmolytic agents of the type described in a recent report from this Laboratory[1] have been extended to the preparation of a series of analogous thiol esters for the purpose of comparative evaluation of their antispasmodic activity. This investigation appeared desirable since data on such thiol esters are relatively limited.[2,3]

In the synthesis of the thiol esters whose salts are listed in Table II, disubstituted acetic acid chlorides were condensed with 2-diethylaminoethanethiol[4] and various pyrrolidylalkanethiols. The latter were prepared from the corresponding alcohols,[5] via the intermediate pyrrolidylalkane chloride hydrochlorides and isothiouronium chloride hydrochlorides recorded in Table I, by the general procedure of Albertson and Clinton.[4] In order to suppress spontaneous oxidation of these thiols, the ethereal extract from the alkaline decomposition of the pyrrolidylalkane isothiouronium salts was dried and treated with the appropriate acid chloride immediately.

Preliminary pharmacological assays by Dr. Milton J. Vander Brook of our Department of Pharmacology indicate that these thiol esters have less activity against acetylcholine chloride induced spasms than the corresponding oxygen esters.

Experimental[6,7]

The examples below illustrate the procedures used for the preparation of the various intermediates and thiol ester salts.

2-(2-Methyl-1-pyrrolidyl)-ethyl Chloride Hydrochloride.—Hydrogen chloride gas was passed into a cooled solution of 51.8 g. (0.4 mole) of 2-(2-methyl-1-pyrrolidyl)-ethanol[5] in 200 ml. of dry benzene until strongly acid. Then 36.3 ml. (0.5 mole) of thionyl chloride was added slowly with cooling in an ice–water-bath. When the addition was complete the solution was heated on a steam-bath for two hours during which time hydrogen chloride and sulfur dioxide were evolved. The chloride hydrochloride crystallized and, after cooling, was collected and washed first with benzene, then with absolute ether, and dried giving a quantitative yield of nearly white crystals, m. p. 183.5–185°. This was used without further purification for the preparation of the isothiouronium salt. An analytical specimen was prepared by recrystallization from isopropyl alcohol using decolorizing charcoal; m. p. 184–185.5°.

2-(2-Methyl-1-pyrrolidyl)-ethyl-isothiouronium Chloride Hydrochloride.—A solution of 46.0 g. (0.25 mole) of the above chloride hydrochloride and 19.0 g. (0.25 mole) of thiourea in 50 ml. of 95% ethanol was refluxed on a steam-bath for twenty hours. The product which separated after cooling was collected, washed successively with ethanol and acetone, and recrystallized from about 250 ml. of 95% ethanol giving 43.3 g. of nearly white crystals, m. p. 216–218°. Dilution of the filtrate with acetone gave an additional 7.9 g., m. p. 215–217°.

2-(2-Methyl-1-pyrrolidyl)-ethyl Phenyl-Δ^2-cyclopentenylthiolacetate Hydrochloride.—In an apparatus designed for continuous extraction[8] of an aqueous solution by ether was placed a solution of 16.9 g. (0.065 mole) of the above isothiouronium salt in 30 ml. of water and the air in the apparatus displaced with nitrogen. A solution of 5.3 g. of sodium hydroxide in 20 ml. of water was added and the mixture extracted continuously with peroxide-free ether for six hours. The ether extract was dried over Drierite, filtered and added to a solution of 13.3 g. (0.06 mole) of phenyl-Δ^2-cyclopentenylacetyl chloride[9] in 50 ml. of dry benzene. The mixture became warm and an oil separated. After refluxing for two hours, the mixture was shaken with ice-water containing a small amount of hydrochloric acid. The ether layer was extracted again with water and the combined aqueous solution washed with ether and made basic with sodium hydroxide. The oily ester which separated was taken up in ether, washed well with water and dried first over sodium sulfate and then over Drierite. The solution was filtered and hydrogen chloride gas introduced until strongly acidic. The hydrochloride separated as a viscous oil which crystallized partly on standing. After decanting the ether, the crude hydrochloride was dissolved in warm ethyl acetate. On cooling it crystallized and was collected, washed with ethyl acetate and dried. It was recrystallized from ethyl acetate giving 7.0 g. of white crystals, m. p. 111–115°.

2-(2-Methyl-1-pyrrolidyl)-ethyl-Δ^2-cyclopentenyl-*n*-propylthiolacetate Acid Citrate.—The hydrochloride cor-

(1) Kolloff, Hunter, Woodruff and Moffett, THIS JOURNAL, **70**, 3862 (1948).

(2) Richardson, U. S. Patent 2,390,555.

(3) Clinton and Salvador, THIS JOURNAL, **68**, 2076 (1946).

(4) Albertson and Clinton, *ibid.*, **67**, 1222 (1945).

(5) Moffett, *J. Org. Chem.*, **14**, 862 (1949).

(6) Melting points and boiling points are uncorrected.

(7) Analyses by Mr. Harold Emerson and staff of our Microanalytical Laboratory.

(8) This apparatus is a modification of that described in "Organic Syntheses," **23**, 49 (1943).

(9) Horclois, *Chemie and industrie*. Special No. 357 (April, 1934).