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.

Acknowledgment.—The authors wish to express their sincere appreciation for the advice and help given them by Dr. C. M. Suter and Dr. J. S. Buck, both of whom were associated with this research. The authors also wish to thank Miss A. Rainey and Miss P. Curran for the great majority of the micro-analyses recorded in this paper.

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

(1) Present address: University of Minnesota, Minneapolis, Minn.

(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).

TABLE I

8-SUBSTITUTED 3-METHYLQUINOLINE DERIVATIVES

Compound	Yield,[c] %	Appearance	Solvent[a]	M. p.,[b] °C.	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Ethyl 3-Methyl-4-hydroxyquinoline-2-carboxylates										
8-Chloro	62	White needles	Sk	88	58.76	4.55	5.27	58.64	4.57	5.63
8-Bromo	59	Pale yellow prisms	aAc	112	50.34	3.90	4.52	50.91	3.93	4.47
8-Methoxy	85	Yell.-white needles	aE	128	64.35	5.78	5.37	64.87	5.80	5.53
8-Ethoxy	73	White prism-needles	aAc	150	65.44	6.23	5.09	65.75	6.88	5.41
8-Methyl	87	Creamy-white needles	aE	126	68.55	6.17	5.71	68.47	6.20	5.88
3-Methyl-4-hydroxyquinoline-2-carboxylic Acids										
8-Chloro	100	Yell.-white microcryst	aP	>285	55.59	3.47	5.89	55.71	3.95	5.95
8-Bromo	91	Yell.-white microcryst	P	d. 234	46.83	2.86	4.97	47.23	2.53	4.73
8-Methoxy	88	Yell.-white microcryst	P	d. 254	61.80	4.75	6.01	62.33	4.73	6.37
8-Ethoxy	90	Fine yellowish needles	P	d. 228	63.15	5.30	5.67	63.48	5.31	5.81
8-Methyl	95	Creamy-white needles	P	d. 244	66.25	5.10	6.45	66.00	4.98	6.66
3-Methyl-4-hydroxyquinolines										
8-Chloro	95	Fine white needles	aAc	220	62.02	4.17	7.24	62.62	4.35	7.05
8-Bromo	92	Fine white needles	aE	223	50.44	3.39	5.88	50.59	3.85	5.64
8-Methoxy	97	Fine white needles	aE	217	69.82	5.82	7.40	70.19	6.07	7.69
8-Ethoxy	95	Fine white needles	aE	204	70.92	6.45	6.89	71.17	6.14	6.85
8-Methyl	96	White prismatic needles	aE	250	76.27	6.40	8.09	76.48	6.74	8.11
3-Methyl-4-chloroquinolines										
8-Chloro	92	White needles	aE	103	56.87	3.34	6.63	56.85	3.65	6.52
8-Bromo	95	White needles	aE	111	46.81	2.75	5.46	47.08	3.23	5.56
8-Methoxy	90	White platelets	aE	84	63.48	6.11	6.74	63.20	6.38	6.79
8-Ethoxy	99	White needles	aE	64	65.01	5.46	6.32	64.85	5.46	6.29
8-Methyl	92	White needles	aE	63	68.94	5.26	7.31	68.74	5.57	7.50
3-Methyl 4-(1-methyl-4-diethylaminobutylamino)-quinolines				(B. p., °C.)						
8-Chloro	80	Golden-yellow oil		206 (0.6 mm.)	68.40	8.46	12.62	68.11	8.53	12.68
8-Bromo	85	Orange-yellow oil		220 (1.5 mm.)	60.31	7.46	11.11	59.96	7.85	11.10
8-Methoxy	78	Orange-yellow oil		201 (0.8 mm.)	72.90	9.56	12.75	72.71	9.29	12.49
8-Ethoxy	89	White micro-cryst	Sk	M. p. 77	73.43	9.68	12.23	[d]	[d]	12.15
8-Methyl	76	Yellow oil		177 (0.5 mm.)	76.63	9.97	13.70	77.06	9.63	13.49

Legend: [a] Ac, acetone; E, ethanol; P, propylene glycol; a, aqueous (usually 20% water), and Sk, Skellysolve A. [b] Corrected. d. = decomposes. [c] Not purified—as used for next stage. [d] C and H analyses not concordant.

usual fashion in medicinal grade mineral oil at 250–255°, and the resulting quinoline esters freed of oil by judicious washing with cold Skellysolve A. Although all of the 8-substituted ethyl 3-methyl-4-hydroxyquinoline-2-carboxylates were considerably more soluble in the Skellysolves than other quinoline esters encountered, this behavior was particularly marked with the 8-bromo and -chloro derivatives. As later found, it was desirable to hydrolyze these esters directly after filtering off the solid from the greater portion of the oil, and then to remove the remaining oil by extraction of the solution of the sodium salt of the acid with ether. This procedure resulted in considerably improving the over-all yields in the synthesis. The crude esters, whether freed from mineral oil or not, were quite satisfactory for the remainder of the synthesis.

3-Methyl-4-(1'-methyl-4'-diethylaminobutylamino)-quinolines.—The 8-substituted 3-methyl-4-(1'-methyl-4'-diethylaminobutylamino)-quinolines were prepared from the above-described quinoline esters by use of the procedure previously outlined.[1a]

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