N,N-dimethylaminoethyl ether (19): In a 500-cc., three-necked flask equipped with a stirrer, condenser and dropping funnel, containing a suspension of sodium amide (from 6.74 g. (0.29 mole) of sodium) in 250 cc. of dry xylene, there was added cautiously at 0° 53 g. (0.286 mole) of phenyl-2-pyridylmethylcarbinol. A vigorous evolution of ammonia occurred and the resulting deep blue reaction mixture was heated for several hours on the steam-bath. Then 32.5 g. (0.30 mole) of β-N,N-dimethylaminoethyl chloride was added and the reaction mixture heated for approximately eighteen hours on the steam-bath. During this time, the deep blue color of the sodium salt of the carbinol was discharged and a turbid brown mixture resulted. The excess sodium amide was decomposed with water, the xylene layer was separated and, after drying, was evaporated *in vacuo*. The crude alkamine ether was fractionated.

The following procedures were used in an attempt to secure ethers II and III. To phenylmagnesium bromide (48.7 g. bromobenzene) in 150 cc. ether, there was added 37.8 g. of 2-acetylthiophene. The reaction product yielded 23.3 g. of a pale yellow liquid, b. p. 100–108° (0.5 mm.).

Anal. Calcd. for $C_{12}H_{10}S$: C, 77.35; H, 5.41. Found: C, 77.26; H, 5.44. The residue from the distillation yielded 13.1 g. of a viscous material, b. p. 185–245 (0.5 mm.) which resinified on standing.

To a sodium amide suspension, from 1.2 g. of a sodium in 250 cc. of toluene, there was added at room temperature 10 g. of 1-phenyl-2-(2-pyridyl)-ethanol. The reaction mixture was heated with stirring on the steam-bath for two hours and then 9 g. of β-dimethylaminoethyl chloride was added. The condensation was carried out in the usual manner and the product distilled; yield 8.4 g.; b. p. 158–162° (2.5 mm.); m. p. 90–91° after recrystallization from aqueous ethanol, mixed m. p. with an authentic sample of α-stilbazole, 90–91°.

Acknowledgment.—We are grateful to Dr. Richard Tislow and Mrs. Annette LaBelle for the pharmacological data reported herein.

Summary

A series of pyridyl-substituted alkamine ethers has been synthesized from pyridyl substituted carbinols and dialkylaminoalkyl halides. In general, the 2-pyridyl substituted alkamine ethers showed a high order of antihistaminic activity whereas the corresponding 3-pyridyl compounds were relatively less active.

BLOOMFIELD, N. J. RECEIVED SEPTEMBER 15, 1948

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Quinolines. VII. Some 3-Methylquinolines

BY EDGAR A. STECK AND LOUIS L. HALLOCK[1]

Potential antimalarials of the 4-amino-3-methylquinoline type have been the subject of considerable investigation in these laboratories.[2-6] The bulk of these studies[2,5] was concerned with the influence of the variation of substituents in the benzenoid moiety upon the schizontocidal action of 4-(4-diethylamino-1-methylbutylamino)-3-methylquinoline derivatives. In the present contribution there are presented data relating to the preparation of 4-(4-diethylamino-1-methylbutylamino)-7-ethoxy-3-methylquinoline and certain experiences in the synthesis of other 3-methylquinolines which were terminated prior to completion because other work intervened.

The preparation of 4-chloro-7-ethoxy-3-methylquinoline, required for reaction with 4-diethylamino-1-methylbutylamine, was accomplished by a modification of the Conrad-Limpach synthesis.[2d] In the cyclization of the anil from 3-phenetidine and ethyl α-ethoxalylpropionate, only one quinoline ester appeared to be formed (*cf.* ref. 2c, d and 5), as in the case of the related methoxy series.[7] The structure of the series (notice Table I) could not be proved unequivocally, for several attempts to oxidize[2c,d] the ethoxy-4-hydroxy-3-methylquinoline or related 2-carboxylic acid gave only 3-phenetidine. There was no comment as to difficulty in the proof of structure of the 7-methoxy analog by oxidation,[7] but the facile decarboxylation of several anthranilic acids has been recorded in the literature recently,[8,9] including 4-methoxyanthranilic acid. The 7-position is assigned to the ethoxy group on the basis that only one product resulted from the pyrolytic cyclization (*cf.* ref. 7) and the ease with which the oxidation product decarboxylated to 3-phenetidine (*cf.* ref. 9).

The work on 3,5/7-dimethylquinoline derivatives was halted when it was learned that Hauser, *et al.*,[7] were engaged in similar studies. 3-Toluidine was employed as the starting material in the Conrad–Limpach synthesis, and the preparation discontinued at the 4-chloro-3,5/7-dimethylquinoline stage. The structure of the series, shown in Table I, was proven by the catalytic dehalogenation of one of the 4-chloroquinoline derivatives to the corresponding dimethylquinoline, previously prepared by Manske.[10] It was of interest that the lower-melting isomer of the 4-chloroquinoline type, here an oil, was the one bearing a methyl group in position 7 (*cf.* ref. 5).

(1) Present address: Commercial Solvents, Inc., Terre Haute, Ind.

(2) Steck, Hallock and Holland, THIS JOURNAL, **68**, (a) p. 129 (1946), (b) p. 132, (c) p. 380, (d) p. 1241.

(3) Huber, Bair, Laskowski, Jackman and Clinton, *ibid.*, **68**, 322 (1946).

(4) Kwartler and Lucas, *ibid.*, **68**, 2395 (1946).

(5) Steck, Hallock, Holland and Fletcher, *ibid.*, **70**, 1012 (1948).

(6) Steck, Hallock and Suter, *ibid.*, **70**, 4063 (1948).

(7) Hauser and co-workers, *ibid.*, **68**, 1232 (1946).

(8) Surrey and Cutler, *ibid.*, **68**, 2570 (1946).

(9) Stephen, Tonkin and Walker, *J. Chem. Soc.*, 1034 (1947).

(10) Manske, Marion and Leger, *Canadian J. Res.*, **20B**, 133 (1942).

TABLE I

SOME 3-METHYLQUINOLINE DERIVATIVES

3-Methyl-quinoline	Yield, %[a]	Appearance	Solvent[b]	M. p., °C.[c]	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Ethyl 4-hydroxy-3-methylquinoline-2-carboxylates										
7-Ethoxy	69[d]	White needles	E	182.5–183	65.44	6.23	5.09	65.48	6.18	5.30
5-Methyl	37	White prismatic needles	E	196.2–196.8	68.55	6.17	5.71	68.54	6.06	5.71
7-Methyl	43	Fine white needles	aAc	159.5–160				68.45	6.26	5.70
4-Hydroxy-3-methylquinoline-2-carboxylic Acids										
7-Ethoxy	96	Yellowish platelets	Pg	245–245.5 d.	63.15	5.30	5.67	63.23	5.00	5.64
5-Methyl	95	White needles	aE	242–243 d.	66.25	5.10	6.45	66.10	5.04	6.88
7-Methyl	98	Pale yellow needles	E	231–232 d.				66.02	5.42	6.54
4-Hydroxy-3-methylquinolines										
7-Ethoxy	86	White needles	E	254–254.5	70.92	6.45	6.89	70.69	6.54	7.05
5-Methyl	81	Fibrous white needles	aE	270–271[e]	76.27	6.40	8.09	76.16	6.28	8.25
7-Methyl	88	White microcrystals	aE	217–218				76.43	6.24	7.91
4-Chloro-3-methylquinolines										
7-Ethoxy	84	White prismatic needles	SA	93.5–94	65.01	5.46	6.32	65.22	5.06	6.58
5-Methyl	88	White prisms	S, SA	62–62.5[e]	68.94	5.26	7.31	68.86	5.63	7.68
7-Methyl	*ca.* 85	Oil[f]								

[a] Yield as employed in next step, being well-purified at ester stage. [b] Legend: Ac = acetone; E = ethanol; Pg = propylene glycol; S = sublimed; SA = Skellysolve A; a = aqueous. [c] Note reference 14; d. = decomposes. [d] Much tar formed during the cyclization. [e] Previously reported by Hauser, *et al.*; the 4-hydroxy compound was recorded as having m. p. 260–261° and the 4-chloro body had m. p. 59–60.5°. [f] Converted directly into the picrate, golden needles from acetone, m. p. 217–218°. *Anal.* Calcd. for $C_{11}H_{10}ClN$, $C_6H_3N_3O_6$: N, 13.36. Found: N, 13.10.

In the hope of obtaining some compounds bearing the 8-iodo-5-methoxy-3-methylquinoline nucleus, 3-amino-4-iodoanisole[11] was condensed with ethyl α-ethoxalylvalerate and cyclized in Dowtherm A.[12,2d] The loss of iodine was noted throughout all of the attempts to form the quinoline ring bearing the desired groups. Purification of the product of cyclization gave only ethyl 4-hydroxy-methoxy-3-methylquinoline-2-carboxylate, as indicated by analyses and comparison with a sample prepared after the method of Hauser.[7]

A re-examination of certain data relating to previous investigations on bz-iodo-3-methylquinolines[2d] was deemed of interest because the iodomethoxy type had a labile iodine atom. The compound formed by the action of 5% sodium hydroxide upon ethyl 4-hydroxy-5-iodo-3-methylquinoline-2-carboxylate was found to contain iodine when boiled with sodium and amyl alcohol. Analyses on this substance were not concordant, as earlier noted.[2d] When the acid was decarboxylated, a loss of iodine did occur, but the analyses indicated an impure substance. At last, treatment with phosphorus oxychloride gave a small amount of 4-chloro-3-methylquinoline[2a] after extensive purification by crystallization and sublimation.

The only compound herein reported which was screened as an antimalarial was 4-(4-diethylamino-1-methylbutylamino)-7-ethoxy-3-methylquinoline (SN-13,573[13]). This compound, although fairly low in activity, was superior to the related methoxy derivative (SN 10,566) and the 6- and 8-ethoxy-4(4-diethylamino-1-methylbutylamino)-3-methylquinolines[2a,b] (SN 9,082 and 12,348).

Experimental[14]

7-Ethoxy-3-methylquinolines.—The application of the Conrad–Limpach synthesis to 3-phenetidine and ethyl α-ethoxalylpropionate followed the usual pattern, and data relating to the intermediates are presented in Table I. Several attempts to prove the structure of these compounds unequivocally by oxidative means[2c,d] failed because the resulting anthranilic acid decarboxylated readily to give only 3-phenetidine. The reaction of 4-chloro-7-ethoxy-3-methylquinoline with 4-diethylamino-1-methylbutylamine in phenol[2] at 170° led to a 76% yield of the 4-(4-diethylamino-1-methylbutylamino) compound. 4-(4-Diethylamino-1-methylbutylamino)-7-ethoxy-3-methylquinoline, SN-13,573, was obtained as a golden oil which boiled at 180–186° (0.05 mm.).

Anal. Calcd. for $C_{21}H_{33}N_3O$: C, 73.43; H, 9.68; N, 12.33. Found: C, 73.45; H, 9.58; N, 12.29.

3,5/7-Dimethylquinolines.—The synthesis of both the 3,5- and 3,7-dimethylquinolines here proceeded from 3-toluidine and ethyl α-ethoxalylpropionate in the customary manner. Hauser, *et al.*,[7] prepared several 3,5-dimethylquinoline derivatives through dehalogenation of 8-chloro-4-hydroxy-3,5-dimethylquinoline. In the present case, the isomeric ethyl 3,5- and 3,7-dimethyl-4-hydroxyquinoline-2-carboxylates proved to be rather recalcitrant of separation. The high-melting isomer, the 3,7-dimethyl compound, was less soluble in 70% acetone, while

(11) During the compilation of these data, the preparation of this compound was reported: Frank, Fanta and Tarbell, THIS JOURNAL, **70**, 2319 (1948).

(12) A commercial heat-transfer liquid consisting of 73.5% diphenyl ether and 26.5% diphenyl.

(13) All drugs identified by Survey Numbers (SN) in the files of the Antimalarial Survey have been systematically tabulated, together with the antimalarial activities, in "Antimalarial Drugs, 1941–1945" (F. Y. Wiselogle, editor), Edwards Bros., Ann Arbor, Mich., 1946.

(14) The melting points and boiling points reported are uncorrected values.

the other was best crystallized from alcohol. In Table I are listed the properties of the compounds involved in proceeding to the 3,5- and 3,7-dimethyl-4-chloroquinolines. The structure of the two series was clarified by dehalogenation of the 4-chloro compound of m.p. 59.5–60° in alcohol containing one equivalent of sodium hydroxide employing Busch–Stöve catalyst[15] under 50 lb./sq. in. hydrogen pressure. The crude product was directly converted to the picrate, which melted at 221° after crystallization from acetone. Manske, *et al.*[10] have given the melting point of 3,5-dimethylquinoline picrate as 220° while that salt of 3,7-dimethylquinoline melted at 244°.

3-Amino-4-iodoanisole in the Conrad–Limpach Synthesis.—4-Amino-3-nitroanisole was diazotized and treated with potassium iodide after the manner of Reverdin[11,16,17] to give 4-iodo-3-nitroanisole in 86–92% crude yield. It crystallized from Skellysolve C or aqueous alcohol as orange needles, m.p. 62.5–63°. The reduction of the nitro group was best accomplished by the method of West[11,18] using aqueous ethanol as the solvent. Crude yields of 65–73% resulted, the 3-amino-4-iodoanisole being a reddish-brown oil. The crude material was used in subsequent work, for while a trial batch gave a fair recovery of a reddish liquid, b.p. *ca.* 90–115° (0.2 mm.), another sample exploded when distillation was attempted, much iodine vapor being noted afterward. This occurrence has also been witnessed recently by Tarbell *et al.*[11]

The condensation of crude 3-amino-4-iodoanisole with ethyl α-ethoxalylpropionate was carried out in the usual manner, the product resulting in 69–80% yield. All attempts to cyclize the anil in Dowtherm A led to copious evolution of iodine vapor. When the crude reaction product was crystallized from ethanol and from acetone several times, using Darco G-60 liberally, fine white needles were obtained, m.p. 192–192.5°. Analysis and mixed melting point with an authentic sample (prepared from 3-anisidine by the method described by Hauser, *et al.*[7]) showed this compound to be ethyl 4-hydroxy-7-methoxy-3-methylquinoline-2-carboxylate. The yields obtained (from the anil) were 52–66%.

(15) Busch and Stöve, *Ber.*, **49**, 1064 (1916).

(16) Reverdin, *ibid.*, **29**, 2595 (1896).

(17) Hata, Tatematsu and Kubota, *Bull. Chem. Soc.* (*Japan*), **10**, 425 (1935).

(18) West, *J. Chem. Soc.*, 494 (1925).

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.35; H, 5.78; N, 5.37. Found: C, 64.45; H, 6.06; N, 5.36.

Further Study of 5-Iodo-3-methylquinolines.—In a previous contribution in this series,[2d] it was reported that a halogen-free compound, m.p. 251° dec., was obtained by the action of boiling 5% caustic upon ethyl 4-hydroxy-5-iodo-3-methylquinoline-2-carboxylate. This substance was re-examined and found to contain iodine when boiled with *n*-amyl alcohol and sodium for some while. The low solubility of the material in the common solvents led to the use of 2-methyl-2,4-pentanediol, but satisfactory analyses could not be obtained. Decarboxylation of the yellow acid in either Dowtherm A or mineral oil led to a white solid which melted vaguely around 286° after crystallization from alcohol. This alleged 4-hydroxy-5-iodo-3-methylquinoline failed to give concordant analyses, but merely indicated that more iodine was lost during the reaction. Ultimately, the 4-hydroxy-3-methylquinoline type so obtained was interacted with phosphorus oxychloride. The result of extensive purification of the product by crystallization from Skellysolve B and sublimation was a small quantity of white needles, m.p. 61.5–62.5°, which was free of iodine. A melting point of 60° has been reported for 4-chloro-3-methylquinoline.[2a]

Acknowledgment.—The authors wish to express their appreciation to Mrs. N. P. Gorman, Mr. E. V. Ryan and Mr. A. J. Holland for technical assistance. All analyses were carried out by the analytical staff of this Institute under the direction of Mr. M. E. Auerbach.

Summary

The preparation of 4-(4-diethylamino-1-methylbutylamino)-7-ethoxy-3-methylquinoline from 3-phenetidine has been described.

The properties of a number of 3,5- and 3,7-dimethylquinoline derivatives have been reported and the structures proven. Certain experiences with iodinated compounds in the Conrad–Limpach synthesis have been described.

RENSSELAER, NEW YORK RECEIVED SEPTEMBER 20, 1948

[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AND THE SCHOOL OF NUTRITION AT CORNELL UNIVERSITY]

Pteridines. IV. Derivatives of 2,4-Diamino-6,7-diphenylpteridine[1]

BY C. K. CAIN, E. C. TAYLOR, JR., AND LOUISE J. DANIEL

In the course of a study of substituted pteridines, it was found that those compounds which have amino groups in both the 2- and 4-positions of the pteridine nucleus exhibit a high degree of antifolic acid activity against several bacteria.[2,3] However, the diaminopteridines studied showed very low solubility in water and in all of the common organic solvents tested. Since it appeared desirable to have available for biological testing compounds of this type which could be administered in aqueous solution, several experiments have been carried out to modify these compounds in such a way that solubility in water or alcohol would result with the retention of a high degree of antifolic acid activity.

Of the various pteridines previously reported,[4] 2,4-diaminophenanthro(9,10-e)pteridine had the maximum antifolic acid activity against *S. faecalis*. The preparation of a derivative of this compound having a sulfonic acid group on the phenanthrene nucleus has been carried out. The resulting compound is fairly soluble in aqueous sodium bicarbonate solution but shows very little antifolic acid activity. Since it was thought for a variety of reasons that 2,4-diamino-6,7-diphenyl-

(1) The work presented in this paper was undertaken in collaboration with the Office of Naval Research, Navy Department, Washington, D. C., and was aided by a grant to Cornell University by the Nutrition Foundation, Inc., New York City. It represents a part of a collaborative project on "Newer Members of the B Group of Vitamins."

(2) Daniel, Norris, Scott and Heuser, *J. Biol. Chem.*, **169**, 689 (1947).

(3) Daniel and Norris, *ibid.*, **170**, 747 (1947).

(4) Mallette, Taylor and Cain, THIS JOURNAL, **69**, 1814 (1947).