[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

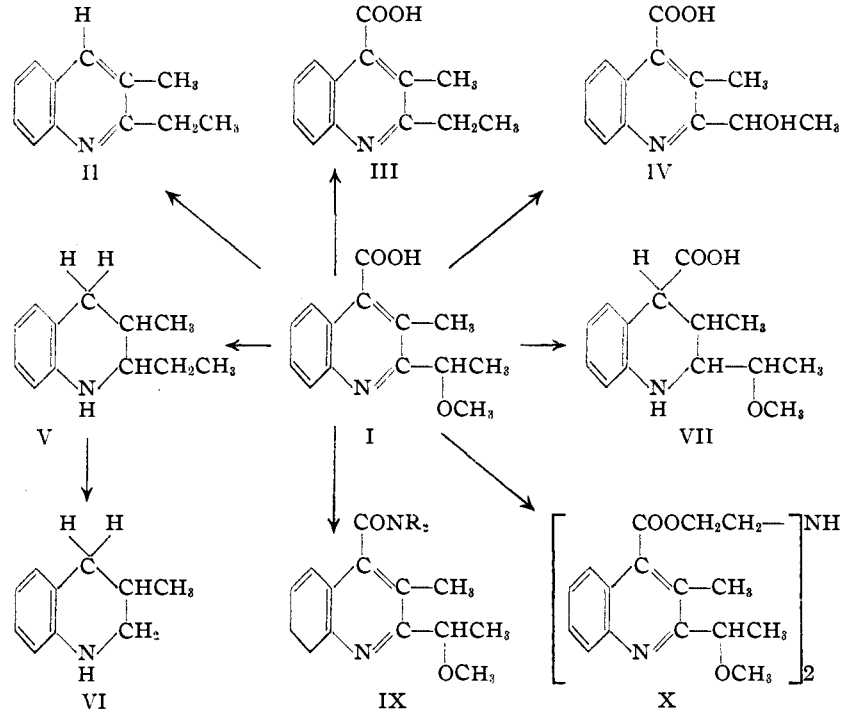
Utilization of Alkoxy Ketones in the Synthesis of Quinolines by the Pfitzinger Reaction. II[1]

BY SHERMAN D. LESESNE[2,3] WITH HENRY R. HENZE

It has been shown recently in this Laboratory that keto ethers[4] can be employed in the synthesis of quinoline derivatives by the Pfitzinger reaction. Thus,[4b] ethoxyacetone and ethoxymethyl ethyl ketone, respectively, were condensed with isatin to produce the corresponding 2-methyl- (or 2-ethyl)-3-ethoxycinchoninic acid. A survey of the literature revealed no record of the preparation of any 2-alkoxyalkylcinchoninic acids.

In the present investigation the Pfitzinger reaction has been extended to include the utilization of alkoxy ketones in the synthesis of 2-alkoxyalkyl and 2-alkoxyalkyl-3-alkylcinchoninic acids. For example, isatin and 1-methoxydiethyl ketone were condensed in potassium hydroxide solution to form 2-(1-methoxyethyl)-3-methylcinchoninic acid (I). Proof of the structure of I was obtained by conversion into 2-ethyl-3-methylquinoline (II)[5] by heating at the melting point of the acid. The decarboxylation which occurred thus was anticipated but the cleavage of the ether linkage and reduction of the carbinol to alkyl was unexpected. Cleavage and reduction without decarboxylation of I to form III was accomplished by heating with hydriodic acid and red phosphorus for six hours. In contrast, when I was heated with concentrated hydrochloric acid only the ether grouping underwent fission and 2-(1-hydroxyethyl)-3-methylcinchoninic acid (IV) resulted. However, by heating for seven days with hydriodic acid and red phosphorus, I was converted into 2-ethyl-1,2,3,4-tetrahydro-3-methylquinoline (V). In turn, V, by action of hydrochloric acid and tin, yielded 1,2,3,4-tetrahydro-3-methylquinoline (VI).[6] Reduction without cleavage was effected by catalytic hydrogenation of I in the preparation of 2-(1-methoxyethyl)-1,2,3,4-tetrahydro-3-methylcinchoninic acid (VII).

By treatment of I with thionyl chloride and subsequent interaction with appropriate secondary amines, three substituted amides (IX) were produced; diethanolamine reacted with the acid chloride of I to form the dicarbethoxyamine (X) rather than an hydroxyethyl amide. 2-(1-Methoxyethyl)-cinchoninic acid (XV) reacted in an analogous manner with the same amines.



In view of the fact that some 2-substituted-cinchoninic acid derivatives are useful as antimalarials,[7] it was thought desirable to include, in this study, the synthesis of bis-2-cinchoninic acid (XI) and 2-phenyl-3-ethylcinchoninic acid (XIII).

(1) Presented before the Division of Organic Chemistry of the American Chemical Society at Memphis, Tenn., April 19–24, 1942.

(2) From the Ph.D. dissertation of S. D. Lesesne, June, 1939.

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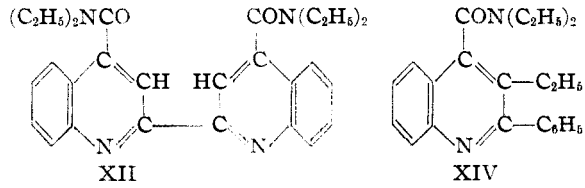
(4) (a) Calaway with Henze, THIS JOURNAL, **61**, 1355 (1939); (b) Cross with Henze, *ibid.*, 2730.

(5) Doebner and v. Miller, *Ber.*, **17**, 1714 (1884).

(6) Braun, Gmelin and Schultheiss, *ibid.*, **56**, 1343 (1923).

(7) von Oettingen, "Therapeutic Agents of the Quinoline Group," Reinhold Publishing Corporation, New York, N. Y., 1935.

Finally, XI and XIII were converted into the corresponding diethylamides, XII and XIV, respectively.



XII XIV

Through the courtesy of Parke, Davis and Company, preliminary pharmacological testing of ten of the new derivatives of cinchoninic acid has been made. The study was made by daily oral treatment for three days of canaries infested with *Plasmodium cathemerium* and led to negative results as far as the antimalarial activity of I, III, XI, XIII, XIV and XVI are concerned. Likewise, against avian malaria compounds XIII and the diethylamides of I and III are inactive. Finally, the diethylamide of bis-2-cinchoninic acid (XII) was found to have no action orally on *Streptococcus viridans* in mice.

Experimental

2-(1-Methoxyethyl)-3-methylcinchoninic Acid (I).—Sixty grams (0.41 mole) of isatin was dissolved in 300 g. of 33% potassium hydroxide solution; 42 g. (0.42 mole) of 1-methoxydiethyl ketone[8] was added and the mixture was heated under a reflux condenser on a steam cone for twenty-four hours. The reaction mixture was diluted with water to a volume of 750 cc., partially decolorized with Norite and filtered while hot. The filtrate was cooled and acidified by addition of 250 cc. of 50% acetic acid solution. After standing in an ice-bath a light cream-colored solid separated. The acid was recrystallized from water in colorless needles melting at 234° (cor.) with decomposition; yield 74 g. (74%). This cinchoninic acid is soluble in alcohol, moderately soluble in acetone, and insoluble in ether and benzene. It readily formed a picrate which melts at 201° (cor.).

Anal. Calcd. for $C_{14}H_{15}NO_3$: neut. equiv., 245.3; C, 68.55; H, 6.16; N, 5.71. Found: neut. equiv., 244.0; C, 68.92; H, 6.17; N, 5.77.

Effect of Heating I.—Fifteen grams of I was heated in a distilling flask in an oil-bath at 250°; the solid first melted, then carbon dioxide was evolved. At the end of twenty minutes gas evolution had ceased and the residual, black liquid was distilled under diminished pressure. There was obtained about 1.5 g. (14% yield) of a clear yellow oil (II) which readily yielded a bright yellow picrate. The latter, after recrystallization from diluted alcohol, melted at 191° (cor.)[9].

Anal. Calcd. for picrate, $C_{18}H_{16}N_4O_7$: C, 54.00; H, 4.03; N, 14.00. Found: C, 53.98; H, 4.03; N, 13.48.

Action of Hydrochloric Acid on I.—Five grams of I was heated with 10 cc. of concentrated hydrochloric acid for forty-eight hours at 100°. Upon neutralization with sodium hydroxide a light cream-colored precipitate formed, which was purified through resolution in alkaline solution and reprecipitation with acetic acid. Thus was obtained 2.7 g. (55% yield) of the mono-hydrate of **2-(1-hydroxyethyl)-3-methylcinchoninic acid** (IV) melting at 265° (cor.). The picrate of this compound has a melting point (explosive!) above 310°.

Anal. Calcd. for $C_{13}H_{13}NO_3 \cdot H_2O$: C, 62.61; H, 6.06; N, 5.62. Found: C, 62.76; H, 5.94; N, 5.50.

Action of Hydriodic Acid on I.—(A) Twelve grams of I, 50 cc. of hydriodic acid (57% strength), and 5 g. of red phosphorus were heated together under a reflux condenser for six hours at 150°. The mixture was made basic with sodium hydroxide and filtered to remove phosphorus. The filtrate was acidified with acetic acid causing precipitation of a white solid, which was filtered, washed with cold water, and after drying weighed 8 g. (78% yield). **2-Ethyl-3-methylcinchoninic acid** (III) melts at 279° (cor.) and is soluble in alcohol, moderately soluble in acetone, and insoluble in ether and benzene. It readily forms a picrate melting at 198° (cor.).

Anal. Calcd. for $C_{13}H_{13}NO_2$: neut. equiv., 215.2; C, 72.54; H, 6.09; N, 6.51. Found: neut. equiv., 213.3; C, 72.52; H, 6.04; N, 6.66.

(B) Twenty grams of I, 100 cc. of hydriodic acid (57% strength), and 5 g. of red phosphorus were heated together for *seven days* at 140–150°. The reaction mixture was made alkaline and subjected to steam distillation. The colorless oil in the distillate was extracted with ether, dried over sodium sulfate and fractionated. Ten grams (70% yield) of **2-ethyl-1,2,3,4-tetrahydro-3-methylquinoline** (V) was obtained; b. p. 253° (716 mm.); $n^{20}D$ 1.5902; d^{20}_4 1.0423; *MR* calcd. 56.51; *MR* found 56.78; picrate (from alcohol) m. p. 188° (cor.).

Anal. Calcd. for $C_{12}H_{17}N$: C, 82.23; H, 9.78; N, 7.99. Found: C, 82.10; H, 9.45; N, 8.03.

Action of Tin and Hydrochloric Acid on V.—Seven grams of V, 40 g. of granulated tin, and 150 cc. of concentrated hydrochloric acid were heated on a steam-bath for twelve hours. At intervals, 50-cc. portions of acid were added to maintain reaction. The reaction mixture was made alkaline and steam-distilled; the distillate was ether extracted, the extract dried and fractionated; 4 g. (68% yield) of **1,2,3,4-tetrahydro-3-methylquinoline** (VI) was collected; b. p. 117° (15 mm.);[10] $n^{20}D$ 1.5536; d^{20}_4 0.9931; *MR* calcd. 47.27; *MR* found 47.50; picrate (from ether) m. p. 159° (cor.).[11]

Catalytic Reduction of I.—Two grams of I in 30 cc. of ethanol was shaken for two hours with 0.05 g. of the Adams catalyst and hydrogen at atmospheric pressure. After filtration from the catalyst, spontaneous evaporation of the filtrate of the solvent yielded **2-(1-methoxyethyl)-1,2,3,4-tetrahydro-3-methylcinchoninic acid** (VII) melting with

(8) (a) Gauthier [*Ann. chim. phys.*, (8) **16**, 322 (1909)] reported only b. p. 133° (729 mm.); (b) Wallace [M.A. thesis, University of Texas, 1936] reported b. p. 154–155° (746 mm.); $n^{20}D$ 0.8913; semicarbazone m. p. 120.5° (cor.).

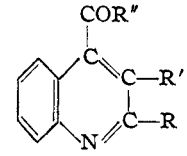
(9) Doebner and v. Miller, ref. 5, recorded m. p. 193° for the picrate of 2-ethyl-3-methylquinoline.

(10) Braun, Gmelin and Schultheiss, ref. 6, reported b. p. 117° (17 mm.).

(11) Braun, Gmelin and Schultheiss, ref. 6, reported m. p. 155°.

TABLE I

AMIDES AND ESTERS OF CERTAIN SUBSTITUTED CINCHONINIC ACIDS



R	R′	R″	Yield, %	M. p., °C. (cor.)	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Picrate m. p., °C. (cor.)
$CH(OCH_3)CH_3$	CH_3	$N(C_2H_5)_2$	55	94	71.95	72.06	8.05	8.13	9.33	9.54	179
$CH(OCH_3)CH_3$	CH_3	$N(CH_2CH_2CH(CH_3)_2)_2$	32	190	74.96	75.22	9.44	9.67	7.29	7.72	200
$CH(OCH_3)CH_3$	CH_3	$N(CH_2CH{=}CH_2)_2$	61	112	74.04	73.68	7.46	7.39	8.64	8.62	146
$CH(OCH_3)CH_3$	CH_3	$(-OCH_2CH_2)_2NH$	52	200	68.67	68.42	6.66	6.60	7.51	7.54	201
C_2H_5	CH_3	$N(C_2H_5)_2$	22	100	75.52	75.68	8.20	8.23	10.36	10.52	174
C_2H_5	CH_3	$N(CH_2CH_2CH(CH_3)_2)_2$	12	132	77.92	78.01	9.67	9.57	7.90	7.83	
C_2H_5	CH_3	$N(CH_2CH=CH_2)_2$	36	liq.	77.52	77.15	7.53	7.70	9.52	9.53	159
C_2H_5	CH_3	$(-OCH_2CH_2)_2NH$	26	295	72.12	71.86	6.66	6.71	8.41	8.49	209
C_6H_5	C_2H_5	$N(C_2H_5)_2$	50	244	79.48	79.53	7.28	7.32	8.43	8.45	179
Diethylamide of bis-2-cinchoninic acid			34	257	73.98	74.04	6.65	6.68	12.33	11.46	

decomposition at 232° (cor.). This acid is soluble in alcohol and acetone, but only moderately so in ether and water. The picrate (from ether) melts at 201° (cor.).

Anal. Calcd. for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.20; H, 7.86; N, 5.50.

Methyl Ester of I.—Five grams of I was heated with 10 cc. of dimethyl sulfate for eight hours at 100°. Upon neutralization of the reaction mixture with sodium hydroxide, a viscous liquid separated and was extracted with petroleum ether. Upon evaporation of the solvent at 0°, **methyl 2-(1-methoxyethyl)-3-methylcinchoninate** crystallized (4.5 g. or 85% yield); m. p. 57° (cor.); picrate (from alcohol) m. p. 179° (cor.).

Anal. Calcd. for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.85; H, 6.49; N, 5.64.

Substituted Amides of I.—In general, 0.02–0.05 mole of I was dissolved in 0.12–0.18 mole of purified thionyl chloride, the mixture was allowed to stand at 0° for thirty minutes, then poured into a mixture of 0.025–0.07 mole of a secondary amine, 0.11–0.26 mole of potassium carbonate and 200–300 cc. of crushed ice. After reaction had ceased the mixture was placed in a separator with 200–300 cc. of ethyl ether and allowed to stand for six hours. The ether layer was removed and dried over sodium sulfate before being concentrated to a small volume by impact of a jet of dry air at 0°. Then 100–200 cc. of petroleum ether was added and evaporation continued until the amide crystallized. Amides were thus prepared from interaction of diethylamine, diisoamylamine and diallylamine, respectively. The compounds are moderately soluble in alcohol and acetone, but insoluble in benzene and water. The melting point of each of these amides, as well as that of the corresponding picrate, is listed in Table I.

In the same manner were prepared three analogous amides from 2-ethyl-3-methylcinchoninic acid (III) and the diethyl amide from bis-2-cinchoninic acid (XI) and 2-phenyl-3-ethylcinchoninic acid (XIII), respectively. Likewise, interaction of diethanolamine and the acid chloride of I and III, respectively, yielded the corresponding dicarbethoxyamines. The melting point data for these amides and ester amines are also included in Table I.

2-(1-Methoxyethyl)-cinchoninic Acid (XV).—This acid was prepared in a manner wholly similar to that of its 3-methyl homolog by interaction of 47 g. of isatin, 34 g. of 1-methoxyethyl methyl ketone,[12] and 200 g. of 33% potassium hydroxide solution. Forty-four grams (60% yield) of the acid was obtained; m. p. 186° (cor.) dec.; a picrate was not produced.

Anal. Calcd. for $C_{13}H_{13}NO_3$: neut. equiv., 231.2; C, 67.52; H, 5.67; N, 6.06. Found: neut. equiv., 229.1; C, 67.35; H, 5.70; N, 6.24.

Twelve grams of XV, 5 g. of red phosphorus and 50 cc. of hydriodic acid (sp. gr. 1.7) were heated at 150° for six hours. Using the procedure for preparation of III, there was obtained 8.2 g. (80% yield) of **2-ethylcinchoninic acid** (XVI) melting at 180° (cor.); a picrate of XII was not obtained.

Anal. Calcd. for $C_{12}H_{11}NO_2$: neut. equiv., 201.2; C, 71.61; H, 5.51; N, 6.96. Found: neut. equiv., 201.2; C, 71.68; H, 5.43; N, 7.13.

When 17 g. of XV was heated at 200° the solid first melted, then decomposed with evolution of carbon dioxide. After twenty minutes the residual black oil was fractionated yielding but 1.5 g. (13% yield) of liquid. The latter was converted into a picrate which melted at 148° (cor.). This temperature compares well with that of the anticipated product of decarboxylation, namely, **2-ethylquinoline.**[13]

Anal. Calcd. for picrate, $C_{17}H_{14}N_4O_7$: C, 52.85; H, 3.65; N, 14.50. Found: C, 52.30; H, 3.62; N, 14.02.

Bis-2-cinchoninic Acid (XI).—A mixture of 40 g. (0.27 mole) of isatin, 12.5 g. (0.14 mole) of acetoin, and 200 g. of 33% potassium hydroxide solution was heated for twenty-four hours at 100°. On cooling the sodium salt of the acid separated and was filtered, redissolved in hot water and acidified with acetic acid. When dry the crude material weighed 28 g. (58% yield) and was purified by dissolution in sodium hydroxide solution and reprecipitation with

(12) Gauthier, ref. 8a, reported only b. p. 114° (727 mm.); Wallace, ref. 8b, reported b. p. 115–116° (739 mm.); $n^{20}D$ 1.3936; d^{20}_4 0.9014; semicarbazone m. p. 141°.

(13) Reher [*Ber.*, **19**, 2997 (1886)] recorded m. p. 147° (cor.).

acetic acid; m. p. 367° (cor.). This acid is insoluble in water and in the common organic solvents; attempts to form a picrate failed.

Anal. Calcd. for $C_{20}H_{12}N_2O_4$: neut. equiv., 172.16; C, 69.76; H, 3.51; N, 8.14. Found: neut. equiv., 174.4; C, 69.64; H, 3.61; N, 8.14.

2-Phenyl-3-ethylcinchoninic Acid (XIII).[14] In a similar manner, from 40 g. (0.27 mole) of isatin, 43 g. (0.27 mole) of phenyl *n*-propyl ketone, and 200 g. of 33% potassium hydroxide solution, was obtained 40 g. (55% yield) of crude acid. After recrystallization from acetone this compound melts at 286° (cor.); the picrate melts at 147° (cor.).

Anal. Calcd. for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.41; H, 5.59; N, 5.04.

Summary

1. The Pfitzinger reaction has been extended to include the production of two cinchoninic acid derivatives containing an alkoxyalkyl substituent at the 2-position through utilization of alkoxyalkyl ketones of type $CH_3OCH(CH_3)COR$.

2. These acids suffer cleavage of their ether linkage by action of concentrated hydriodic acid and red phosphorus, yet resist reduction.

3. The acids are decarboxylated by heating above their melting points, and, by action of tin with hydrochloric acid, undergo reduction of the pyridine nucleus and dealkylation of the ether group.

4. Bis-2-cinchoninic acid and 2-phenyl-3-ethylcinchoninic acid have been prepared and converted into their diethylamides.

5. Several substituted amides of these cinchoninic acids have been prepared and shown elsewhere not to possess antimalarial activity.

(14) Listed by von Oettingen, ref. 7, page 92.

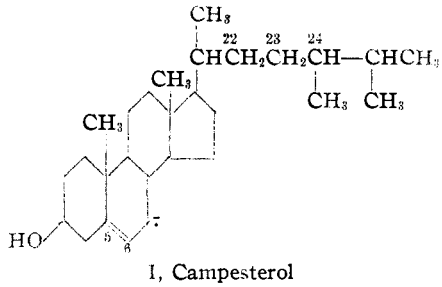
AUSTIN, TEXAS RECEIVED MAY 18, 1942

[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH, DIVISION OF ORGANIC CHEMISTRY]

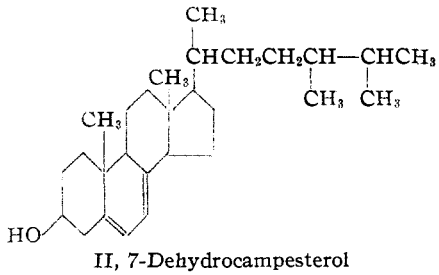
7-Dehydrocampesterol, a New Provitamin D

BY WILLIAM L. RUIGH

The relationship between the structure of the side chain of the D vitamins and their antirachitic activity has been the subject of a number of investigations. The isolation[1] of a new phytosterol, campesterol (I), and the determination of its structure[2] as the C-24 epimer of Δ^5-ergostenol, suggested a new approach to the problem.



I, Campesterol



II, 7-Dehydrocampesterol

Campesteryl acetate was converted by the conventional method[3] via the 7-keto compound into 7(α)-benzoxycampesteryl benzoate. The usual method of preparing 7-dehydrosterols was modified at this point by selectively hydrolyzing the dibenzoate to the 7-monobenzoate and cleaving the latter into benzoic acid and free 7-dehydrocampesterol[4] II. Irradiation of this compound with ultraviolet light gave a resin, the antirachitic activity of which determined by the line test on rats was 725,000 international units per gram. The product obtained from ergosterol under identical conditions assayed at 7,000,000 I. U. per gram corresponding to a yield of 17.5% vitamin D_2 (40,000,000 I. U. per gram). Assuming the same extent of conversion in both cases the potency of the vitamin from 7-dehydrocampesterol is estimated to be 4,100,000 I. U. per gram, which is thus only 10% of the potency of vitamin D_2. Due to lack of sufficient material no attempt was made to isolate the new vitamin in crystalline form.

Vitamin D_4, prepared from 22,23-dihydroergosterol by Windaus and Trautmann,[5] was reported to have from 20,000,000 to 30,000,000

(1) Fernholz and MacPhillamy, THIS JOURNAL, **63**, 1155 (1941).
(2) Fernholz and Ruigh, *ibid.*, **63**, 1157 (1941).
(3) Windaus, Lettré and Schenck, *Ann.*, **520**, 98 (1935).
(4) Wintersteiner and Ruigh, THIS JOURNAL, **64**, 1177 (1942).
(5) Windaus and Trautmann, *Z. physiol. Chem.*, **247**, 185 (1937).