[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF ST. JOHN'S UNIVERSITY AND THE RESEARCH LABORATORIES OF CHEMO PURO MANUFACTURING CORPORATION]

SOME ALKYL ESTER AND CARBAMATE DERIVATIVES OF 3-HYDROXY-2-PHENYLQUINOLINE

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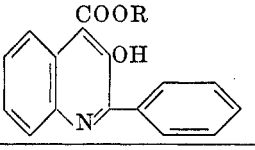
Beyer and co-workers (2) reported that 3-hydroxy-2-phenylcinchoninic acid (HPC) possesses a multiplicity of pharmacodynamic actions, such as anti-diuretic effect, depression of the cardiovascular system, and inhibition of intestinal activity. This compound and some derivatives were reported by several investigators, for example, Marshall and co-workers, and Bertelli (1, 9, 10).

In order to extend the knowledge of 3-hydroxy-2-phenylcinchoninic acid type compounds, a series of normal alkyl esters were prepared in the hope that the pharmacological properties would be retained with diminished toxicity. The synthesis of the esters was accomplished in two ways: (a) By reacting 3-hydroxy-2-phenylcinchoninic acid with the corresponding alcohol in the presence of sulfuric acid catalyst, and/or (b) By reacting the silver salt of 3-hydroxy-2-phenylcinchoninic acid with alkyl halides. The results are summarized in Table I.

TABLE I

n-ALKYL ESTERS OF 3-HYDROXY-2-PHENYLCINCHONINIC ACID

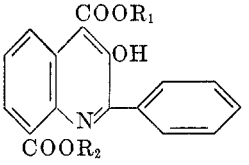


No.	R	Color of Needles	Yield,[a] %	M.P., °C.[b]	Empirical Formula	Analysis[c]					
						Carbon		Hydrogen		Nitrogen	
						Calc'd	Found	Calc'd	Found	Calc'd	Found
I	CH_3	Light yellow	38	104–105	$C_{17}H_{13}NO_3$	73.09	72.93	4.69	4.75	5.02	4.91
II	C_2H_5[d, g]	Lemon yellow	41	110–111	$C_{18}H_{15}NO_3$	73.71	73.94	5.15	4.99	4.71	4.80
III	*n*-C_3H_7	Pale yellow	48	75.3–75.5	$C_{19}H_{17}NO_3$	74.24	74.43	5.56	5.50	4.56	4.52
IV	*n*-C_4H_9	Light yellow	29	74.5	$C_{20}H_{19}NO_3$	74.76	74.89	5.96	6.03	4.36	4.29
V	*n*-C_5H_{11}	Light yellow	24	73.5–74.0	$C_{21}H_{21}NO_3$	75.17	75.18	6.43	6.24	4.18	4.31
VI	Ag.	Light brown	75	221.5[e]	$C_{16}H_{10}AgNO_3$[f]	51.61	51.60	2.71	2.62	—	—

[a] The yields reported are for the purified compounds. [b] The melting points are the corrected values obtained on the pure material. [c] The found values are the average of duplicate analysis. [d] This ester was reported by Dearborn (5) but no physical properties were given. [e] Melted with decomposition. [f] Anal. Calc'd: Ag, 29.00. Found: Ag, 28.87. [g] This ester was prepared by an alternative method from the silver salt and ethyl bromide.

TABLE II

n-ALKYL ESTERS OF 3-HYDROXY-2-PHENYLQUINOLINE-4,8-DICARBOXYLIC ACID AND ITS SILVER SALT

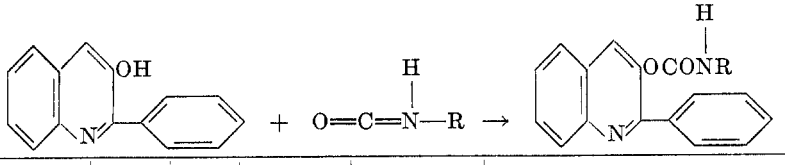


No.	$R_1 = R_2$	Crystal Color	Yield,[a] %	M.P., °C.[b]	Empirical Formula	Analysis[c]					
						Carbon		Hydrogen		Nitrogen	
						Calc'd	Found	Calc'd	Found	Calc'd	Found
VIII	CH_3[d]	Orange	46	118.5	$C_{19}H_{15}NO_5$	67.65	67.60	4.47	4.62	4.15	4.20
IX	C_2H_5[d]	Dark yellow	55	121.0	$C_{21}H_{19}NO_5$	69.03	69.21	5.20	5.24	3.80	3.76
X	*n*-C_3H_7	Light yellow	42	86.5–87.0	$C_{23}H_{23}NO_5$	70.12	70.16	5.90	6.05	3.56	3.51
XI	*n*-C_4H_9	Lemon	46	59.5–60.0	$C_{25}H_{27}NO_5$	71.21	71.39	6.46	6.56	3.32	3.18
XII	Ag	Dark brown	65	>312	$C_{17}H_9Ag_2NO_5$[e]	38.04	38.17	1.73	1.80		

[a] The yields reported are for the purified compounds. [b] The melting points are the corrected values obtained on the pure material. [c] The found values are the average of duplicate analysis. [d] Reported previously in the privately published M.S. thesis of Mr. P. S. Forgione at St. John's University dated May 1952. Recently reported in the published work of Cragoe, *et al.* (4) who found the melting point of IX to be 111–113°. Our method differed from Cragoe, *et al.* [e] *Anal.* Calc'd: Ag, 41.26. Found: Ag, 41.31.

TABLE III

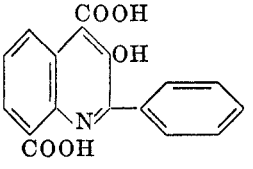
CARBAMATE DERIVATIVES OF 3-HYDROXY-2-PHENYLQUINOLINE



No.	R	Crystal Color	Yield,[a] %	M.P., °C.[b]	Empirical Formula	Analysis[c]					
						Carbon		Hydrogen		Nitrogen	
						Calc'd	Found	Calc'd	Found	Calc'd	Found
XIII	C_6H_5	White	27	162.0	$C_{22}H_{16}N_2O_2$	77.61	77.48	4.74	4.59	8.24	8.34
XIV	α-$C_{10}H_7$	Light tan	34	143–144	$C_{26}H_{18}N_2O_2$	79.97	79.95	4.65	4.85	7.17	7.20
XV	β-$C_{10}H_7$	Light tan	90	181.0–181.5	$C_{26}H_{18}N_2O_2$	79.97	80.01	4.65	4.58	7.17	7.26

[a] The yields reported are for the purified compounds. [b] The melting points are the corrected values obtained on the pure material. [c] The found values are the average of duplicate analysis.

In addition to 3-hydroxy-2-phenylcinchoninic acid, considerable interest has been shown in 3-hydroxy-2-phenylquinoline-4,8-dicarboxylic acid (VII, 4) because of similar pharmacological activity. Several normal alkyl esters of this compound were prepared by method (a) already described. In addition, the di-silver salt of 3-hydroxy-2-phenylquinoline-4,8-dicarboxylic acid was synthesized. The results are summarized in Table II.



VII

Certain carbamates have been shown to have an inhibiting effect on cancerous tissue, for example, in the investigation of Bucher (3). Accordingly some carbamates of 3-hydroxy-2-phenylquinoline were prepared using aryl isocyanates in the hope that they would show similar activity. The results are summarized in Table III.

EXPERIMENTAL

DERIVATES OF 3-HYDROXY-2-PHENYLCINCHONINIC ACID

3-Hydroxy-2-phenylcinchoninic acid (*HPC*). This compound was prepared by two methods: (a) Hanns and Frankel (7) from isatin, potassium hydroxide, and phenacyl bromide in 17% yield; (b) Marshall and Blanchard (8) modified by using phenacyl acetate instead of phenacyl bromide. In this way a yield of 79% was obtained.

Silver 3-hydroxy-2-phenylcinchoninate (VI). 3-Hydroxy-2-phenylcinchoninic acid (2 g., 0.006 mole) suspended in 40 ml. of water was neutralized with dilute ammonium hydroxide (39 ml. water to 1 ml. of concentrated ammonia). To this solution was added with vigorous shaking 0.3 g. of silver nitrate (slight excess) in 30 ml. of water. The heavy yellow precipitate was washed free of silver ion as noted by negative test on washings with dilute hydrochloric acid, and then dried in the dark over sulfuric acid.

Methyl 3-hydroxy-2-phenylcinchoninate (I). 3-Hydroxy-2-phenylcinchoninic acid (2 g., 0.006 mole) was dissolved in 10 ml. of absolute methanol (0.2 mole) and mixed with 0.5 ml. of concentrated sulfuric acid. The mixture was refluxed five hours on the steam-bath. After cooling and diluting with 30 ml. of cold water, an oily layer formed which hardened upon stirring. The mixture then was neutralized with ammonia, and extracted with 60 ml. of ether. The ether extract was washed with 10 ml. water and dried over potassium carbonate. Needles separated after concentrating the ether solution to 10 ml.

Ethyl 3-hydroxy-2-phenylcinchoninate (II). *Method* (*a*): 3-Hydroxy-2-phenylcinchoninic acid (2 g., 0.006 mole) in 10 ml. of absolute ethanol (0.2 mole) and 0.6 ml. of concentrated sulfuric acid were refluxed on the steam-bath for five hours, and the product was recovered in a fashion similar to that described for the methyl ester. *Method* (*b*): Silver 3-hydroxy-2-phenylcinchoninate (0.2 g.) and 2 ml. of dry ethyl bromide suspended in 50 ml. of dry benzene were refluxed for two hours. After overnight standing, the mixture was filtered and concentrated to 10 ml. This concentrate was humidified over 3 ml. of water for a few days, and long light yellow crystals precipitated.

n-Propyl (III), *n-butyl* (IV), *and n-amyl* (V) derivatives of 3-hydroxy-2-phenylcinchoninic acid were prepared with very slight variations in a manner similar to that described for the methyl ester.

DERIVATIVES OF 3-HYDROXY-2-PHENYLQUINOLINE-4,8-DICARBOXYLIC ACID

3-Hydroxy-2-phenylquinoline-4,8-dicarboxylic acid was prepared according to the method of Marshall and co-workers (9) from phenacyl acetate and 2,2-diketoindoline-7-carboxylic acid in 83% yield.

Dimethyl 3-hydroxy-2-phenylquinoline-4,8-dicarboxylate (VIII). 3-Hydroxy-2-phenylquinoline-4,8-dicarboxylic acid (1 g., 0.003 mole), 10 ml. of absolute methanol, and 0.5 ml. of concentrated sulfuric acid were refluxed on the steam-bath for 6 hours. After cooling and diluting with 30 ml. of water, the solution was made alkaline with ammonium hydroxide extracted with 75 ml. of ether. The ether extract was washed with 10 ml. water, dried over potassium carbonate, and concentrated to 10 ml. After several hours standing, orange crystals precipitated, which were recrystallized from ethanol.

Diethyl (IX), *dipropyl* (X), *and dibutyl* (XI) derivatives of 3-hydroxy-2-phenylquinoline-4,8-dicarboxylic acid were prepared with very slight variations in a manner similar to that described for the dimethyl ester.

Silver 3-hydroxy-2-phenylquinoline-4,8-dicarboxylate (XII). 3-Hydroxy-2-phenylquinoline-4,8-dicarboxylic acid (1 g., 0.003 mole) in 40 ml. of water was neutralized with dilute ammonium hydroxide (30 parts of water to 1 part of concentrated ammonia). To this solution was added a slight excess of a silver nitrate solution (0.3 g. of silver nitrate in 30 ml. of water). The product was recovered in a fashion similar to that for the silver 3-hydroxy-2-phenylcinchoninate.

CARBAMATE DERIVATIVES OF 3-HYDROXY-2-PHENYLQUINOLINE

3-Hydroxy-2-phenylquinoline was prepared by decarboxylation of 3-hydroxy-2-phenylcinchoninic acid in nitrobenzene according to the method of Dilthey and Thelen (6).

2-Phenylquinoline-3-phenylcarbamate (XIII). 3-Hydroxy-2-phenylquinoline (0.5 g.), 0.5 ml. of phenyl isocyanate, 5 ml. of dry benzene, and 2 drops of pyridine catalyst were reluxed for 10 minutes in an atmosohere protected with a calcium chloride tube. The benzene solution was diluted with 30 ml. more of benzene, filtered, and concentrated to 10 ml. At this point a gray solid, m.p. 162–170° precipitated. The precipitate was extracted with 25 ml. of carbon tetrachloride; the extract was filtered and evaporated to dryness. The residue was taken up in 20 ml. of ethyl acetate and then precipitated by the addition of 10 ml. of petroleum ether.

2-Phenylquinoline-3-(α-naphthyl)carbamate (XIV) *and 2-phenylquinoline-3-(β-naphthyl) carbamate* (XV) were prepared with very slight variations in a manner similar to that described for the phenyl carbamate.

SUMMARY

Five esters containing methyl, ethyl, *n*-propyl, *n*-butyl, and *n*-amyl radicals, and one silver salt of 3-hydroxy-2-phenylcinchoninic acid were prepared. Also the dimethyl, diethyl, di-*n*-propyl and di-*n*-butyl esters, and the silver salt of 3-hydroxy-2-phenylquinoline-2,8-dicarboxylic acid were synthesized. In addition three carbamate derivatives of 3-hydroxy-2-phenylquinoline, namely, the phenyl, α-naphthyl and β-naphthyl, were prepared.

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NOTICE TO AUTHORS

On and after September 1, 1955, the Journal will accept *Notes*; the Journal will accept *Communications to the Editor* received on or after November 1, 1955 for publication in Volume 21. See revised Notice to Authors for details.

Effective with Volume 21, the Journal will use a double column format with a page size approximately 6½″ by 9″. Authors should consider this in connection with graph sizes, and table compositions.