Anal. Calcd. for $C_{10}H_8O_4$: C, 62.49; H, 4.20. Found: C, 62.69; H, 4.64.

Summary

1. The condensation of ethyl cyanoformate with alkyl derivatives of resorcinol has been used to prepare a number of new 2,4-dihydroxyalkylphenylglyoxylic acids.

2. The use of ethyl cyanoformate is proposed as a general method for introducing the ketocarboxyl (COCOOH) group into activated positions on aromatic nuclei.

3. All hydroxyphenylglyoxylic acids prepared in this work have been subjected to antibacterial and antifungal testing but none showed exceptional activity.

BETHLEHEM, PENNSYLVANIA RECEIVED JUNE 9, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE GEORGIA SCHOOL OF TECHNOLOGY]

Alkoxyaryloxyketones and their Condensation with Isatins

BY R. L. SUBLETT AND PAUL K. CALAWAY

To continue our work[1,2] on the preparation of keto ethers and their conversion into substituted quinoline acids we have prepared a series of ketones from alkoxyphenols by the procedure of Hurd and Perletz.[3] The resulting alkoxyaryloxyketones have been condensed with both isatin and 5-methylisatin, by the method of Pfitzinger,[4] to produce 3-alkoxyaryloxy-4-quinaldinecarboxylic acids.

The yields of the ketones prepared ranged from 47.6%, in the case of the 2-methoxy-4-methylphenoxyacetone, to 73% for the 4-propoxyphenoxyacetone. All of the ketones were obtained, after purification, as light yellow, low-melting solids, which darkened on standing.

The potassium salts of the quinaldinecarboxylic acids were salted out by high concentrations of potassium hydroxide. In every instance, decarboxylation of these acids was observed to start well below the melting point, hence melting point values changed with the rate of heating and are of little significance.

Experimental

Preparation of Alkoxyaryloxyacetones.—The procedure for the condensation of chloroacetone with the alkoxyphenols was based on the method of Hurd and Perletz.[3]

To a vigorously stirred and refluxing suspension of 0.4 mole of the alkoxyphenol and 57 g. (0.41 mole) of anhydrous potassium carbonate in 150 ml. of dry acetone was added over a period of thirty minutes a solution of 50 g. (0.54 mole) of chloroacetone and 3 g. of potassium iodide in 50 ml. of dry acetone. The chloroacetone mixture had been allowed to stand for twenty hours prior to addition. After refluxing for seven hours, stirring was continued for an additional twenty hours at room temperature. The mixture was filtered and the salt washed well with dry acetone. To obtain the ketone from the filtrate it was diluted with water and cooled with ice. The precipitate was recrystallized twice from methanol and water, and again from cyclohexane. The essential data on the ketones and derivatives are tabulated in Table I.

TABLE I

ALKOXYARYLOXYACETONES, $CH_3COCH_2OC_6H_3R'OR''$

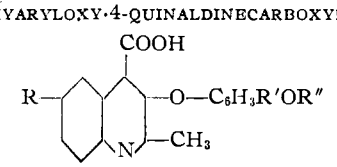
R'	R''	Yield, %	M. p., °C.	2,4-Dinitrophenylhydrazone	Semicarbazone
H	4-CH_3	64	48.5	149	192.3
H	4-C_2H_5	62	35.5	105.5	192
H	4-C_3H_7	73	39	91.5	188.8
H	4-C_4H_9	69	37	153	187.8
4-CH_3	2-CH_3	48	28.5	136	153

Preparation of 3-(4-Methoxyphenoxy)-4-quinaldinecarboxylic Acid.—Fourteen and seven-tenths grams (0.1 mole) of isatin was dissolved in 200 ml. of 33% aqueous potassium hydroxide solution and 17 g. (0.1 mole) of 4-methoxyphenoxyacetone was added. The resulting mixture was heated under reflux on the steam-bath for four hours, and upon cooling a solid cake of potassium 3-(4-methoxyphenoxy)-4-quinaldinecarboxylate separated in the reaction flask. The latter was disintegrated and dissolved in 800 ml. of hot water. The resulting solution was boiled with Nuchar, filtered, cooled in ice, and the quinoline acid precipitated by the addition of acetic acid (1:1). The product was separated by filtration, suspended in 600 ml. of hot water, and converted into the soluble potassium salt by the addition of 33% potassium hydroxide. The treatment with Nuchar was repeated, and 23 g. (74% yield) of the purified acid was obtained. The product was dried over phosphorus pentoxide in a vacuum desiccator.

The remaining 3-alkoxyaryloxy-4-quinaldinecarboxylic acids were formed in essential accordance with this general procedure. In each case a small sample was recrystallized from a large quantity of water and this material used for

TABLE II

3-ALKOXYARYLOXY-4-QUINALDINECARBOXYLIC ACIDS



R	R'	R''	Yield, %	M. p. °C. (dec.)	Nitrogen, % Calcd.	Found
H	H	4-CH_3	74	215	4.56	4.20
H	H	4-C_2H_5	56	214	4.33	4.19
H	H	4-C_3H_7	70	208	4.15	4.14
H	H	4-C_4H_9	77	150	3.99	3.70
H	4-CH_3	2-CH_3	75	232	4.33	4.14
CH_3	H	4-CH_3	67	234	4.33	4.25
CH_3	H	4-C_2H_5	64	198	4.15	4.30
CH_3	H	4-C_3H_7	62	204	3.99	4.01
CH_3	H	4-C_4H_9	60	193	3.83	3.85
CH_3	4-CH_3	2-CH_3	54	242	4.15	4.19

(1) Knight, Porter and Calaway, THIS JOURNAL, **66**, 1893 (1944).
(2) Newell and Calaway, *ibid.*, **69** 116 (1947).
(3) Hurd and Perletz, *ibid.*, **68**, 38 (1946).
(4) (a) Pfitzinger, *J. prakt. Chem.*, **33**, 100 (1886); (b) **38**, 582 (1888); (c) **56**, 283 (1897).

the nitrogen analysis. Table II contains the data on these preparations.

Summary

Pfitzinger's method has been extended to include the utilization of alkoxyaryloxyacetones in the synthesis of ten substituted quinoline acids from isatin and 5-methylisatin, respectively.

ATLANTA, GEORGIA RECEIVED SEPTEMBER 5, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF PHYSIOLOGICAL CHEMISTRY, THE JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE]

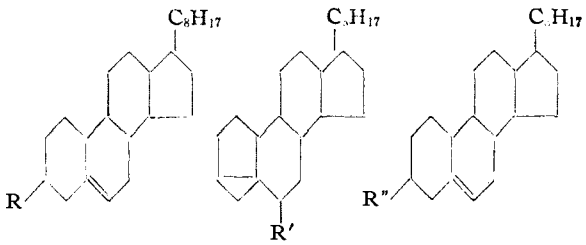
Some Reactions of Cholesteryl *p*-Toluenesulfonate[1]

BY HERBERT MCKENNIS, JR.

In a continuation of studies[2] on the relationship of the structure of cholesterol to its ability to promote growth of *Attagenus* larvae, a number of cholestene derivatives were desired. Cholesteryl *p* toluenesulfonate has been employed successfully in the preparation of 3-alkoxycholestenes,[3] 3-iodocholestene,[4] and a number of other derivatives.

The facile preparation of cholesteryl ethers by refluxing solutions of the *p*-toluenesulfonyl ester of cholesterol in an excess of various alcohols suggested the study of the possible reaction with corresponding mercaptans. This was of interest as a possible synthetic route to thioethers of cholesterol. Additional knowledge of the reactivity of cholesteryl *p*-toluenesulfonate was also desirable since we had planned to study the effect of this compound upon the growth of larvae.

Since *n*-propyl mercaptan has a boiling point quite close to that of methyl alcohol the former was selected for a preliminary study. Attempts to bring about the reaction of cholesteryl *p*-toluenesulfonate (I) with an excess of the mercaptan at reflux temperature for short periods were unsuccessful. After a three-hour period the ester was recovered in quantitative yield. Under similar conditions methanol reacts readily and cholesteryl methyl ether (IIIa) is easily obtained.



I II III

I R = $-OSO_2C_6H_4CH_3$ IIc R′ = $-CH(COOH)_2$
IIa R′ = $-OCH_3$ IIIa R″ = $-OCH_3$
IIb R′ = $-OOCCH_3$ IIIb R″ = $-CH(COOH)_2$

One suggested reason for the marked difference in reactivity was the more strongly acidic character of the thioalcohol. That this alone cannot explain the results is clearly shown in experiments in which thiophenol and benzyl mercaptan were the alcohols employed. Thiophenol, kindly supplied by Dr. E. Emmett Reid, reacted readily with the tosyl ester to yield a bis-(phenylthio)-compound which is tentatively assigned the structure of 3,5-bis-(phenylthio)-cholestane. Benzyl mercaptan also reacted. The product in this instance was not, however, obtained in pure condition.

In view of the marked differences in reactivity observed it became desirable to know whether or not *n*-propyl alcohol itself would react under conditions drastic enough for the seemingly quantitative reaction with methanol, but not sufficiently drastic or prolonged for significant reaction with *n*-propyl mercaptan. The reaction with *n*-propanol under comparable conditions proceeded readily, and cholesteryl *n*-propyl ether was obtained in good yield.

In contrast to the marked reactivity of cholesteryl *p*-toluenesulfonate with methanol, propanol, thiophenol, and benzyl mercaptan at temperatures below 70°, the ester appeared not to react at all when heated with an excess of benzylamine at 70° for two hours. At reflux temperature (185°) reaction took place with the formation of an N-benzylamino compound which is assigned the quasi-committal name, N-benzylcholesterylamine, in accordance with the precedential designation, N-phenylcholesterylamine, for the product obtained by the analogous reaction of aniline and cholesteryl *p*-toluenesulfonate.[5] Under alkaline conditions cholesteryl *p*-toluenesulfonate reacts with methanol[3a] and other alcohols[3b] to give ethers, isomeric with the compounds obtained in the absence of alkali, for which structure IIa has been proposed.[6] Wagner-Jauregg and Werner[7] have found that a comparable situation obtains when cholesteryl chloride or bromide is heated with methanol. When the reaction was carried out in the presence of potassium acetate, *i*-cho-

(1) Aided by a grant from the John and Mary R. Markle Foundation.

(2) McKennis, *J. Biol. Chem.*, **167**, 645 (1947).

(3) (a) Stoll, *Z. physiol. Chem.*, **207**, 147 (1932); (b) Beynon, Heilbron and Spring, *J. Chem. Soc.*, 907 (1936).

(4) Helferich and Gunther, *Ber.*, **72**, 338 (1939).

(5) (a) Bátyka, *Magyar Biol. Kutató Inézet Munkái*, **13**, 334 (1941); *C. A.*, **36**, 484 (1942); (b) Müller and Bátyka, *Ber.*, **74**, 705 (1941).

(6) Wallis, Fernholz and Gephart, THIS JOURNAL, **59**, 137 (1937); see also, Ford and Wallis, *ibid.*, **59**, 1415 (1937); Ford, Chakravorty and Wallis, *ibid.*, **60**, 413 (1938); and Butenandt and Suranyi, *Ber.*, **75**, 591 and 597 (1942), for additional evidence in support of this structure.

(7) Wagner-Jauregg and Werner, *Z. physiol. Chem.*, **213**, 119 (1932).