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

The Synthesis of Quinolines from Aryloxyketones by the Method of Pfitzinger

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In a recent investigation[2] in this Laboratory we have utilized the tolylthiopropanones in the preparation of substituted quinoline acids by the method of Pfitzinger.[3] The availability of the cresols suggested the preparation of the toloxypropanones[4] and their ultimate condensation with isatin and 5-methylisatin, respectively, to produce six substituted cinchoninic acids. We have studied also the condensation of 5-methylisatin with both α- and β-naphthoxyacetone.[5]

In previous papers[6,7] it has been demonstrated that the product of condensation of isatin with aryloxy ketones has been the 3-aryloxy-4-quinaldinecarboxylic acid rather than the isomeric 2-aryloxymethylcinchoninic acid.

The aryloxy ketones used in this investigation were prepared from the corresponding phenols and chloroacetone by the method of Hurd and Perletz.[8] The yields ranged from 57% of the theoretical, in the case of the *m*-toloxyacetone, to 97% for the β-naphthoxyacetone.

The potassium salts of the quinaldinecarboxylic acids prepared showed a tendency to foam in water solution and were salted out by high concentrations of potassium hydroxide. All of the acids exhibited a tendency to hold water of crystallization.[2] This water was removed by drying for several days in a vacuum desiccator over phosphorus pentoxide. Decarboxylation of the compounds was observed to start around 175°; hence melting point values varied with the rate of heating.

Experimental

Preparation of Aryloxyacetones.—The procedure used for the condensation of chloroacetone with phenols was based on the method of Hurd and Perletz.[8]

To a vigorously stirred and refluxing suspension of 0.41 mole of the phenol and 57 g. (0.41 mole) of anhydrous potassium carbonate in 150 ml. of dry acetone was added over a period of one hour a solution of 50 g. (0.54 mole) of chloroacetone and 3 g. of powdered potassium iodide in 50 ml. of dry acetone. The chloroacetone solution had been allowed to stand for twenty-four hours prior to addition. After refluxing for six hours, stirring was continued at room temperature for an additional twenty hours. The mixture was subjected to filtration, the precipitate washed well with dry acetone and the filtrate and washings combined. The solvent was distilled off and the residue distilled under diminished pressure. Table I contains the data on these preparations.

TABLE I

ARYLOXYACETONES, $ArOCH_2COCH_3$

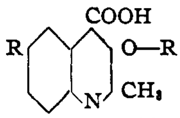
ArO	B. p. or m. p., °C.	Pressure, mm.	Yield, %
p-Toloxy	108–112	6	58
m-Toloxy	110–111	5	57
o-Toloxy	105–106	5	71
α-Naphthoxy	156–165	9	31
β-Naphthoxy	72–73		97

Preparation of 3-*m*-Toloxy-4-quinaldinecarboxylic Acid.—Seven and thirty-five hundredths grams (0.05 mole) of isatin was dissolved in 125 ml. of 33% aqueous potassium hydroxide solution, and 8.2 g. (0.05 mole) of *m*-toloxyacetone was added. The resulting mixture was heated under reflux on the steam-bath for six hours, and, upon cooling, a solid cake of potassium 3-*m*-toloxy-4-quinaldinecarboxylate separated. The latter was disintegrated and dissolved in 500 ml. of hot water. The resulting solution was boiled with Nuchar, filtered, cooled in ice and the crude acid precipitated by the addition of acetic acid (1:1). The quinoline acid was separated by filtration, suspended in 500 ml. of hot water, and converted into the soluble potassium salt by the addition of the calculated amount of 33% potassium hydroxide solution. The solution was again treated with Nuchar, filtered, and made barely acidic by the addition of acetic acid. The quinoline acid was separated by filtration, washed twice with 100-ml. portions of cold water, suspended in 400 ml. of boiling water for forty-five minutes, and filtered while hot. Nine and eight-tenths grams (67% yield) of the 3-*m*-tolyloxy-4-quinaldinecarboxylic acid was obtained. The product melted with decomposition at 224°. Dried over anhydrous calcium chloride the acid retained two molecules of water of hydration (as indicated by analytical data for nitrogen content). This water was removed by drying over phosphorus pentoxide in a vacuum desiccator.

The remaining 3-toloxy-4-quinaldinecarboxylic acids were formed in essential accordance with this general procedure. Table II contains the data on these preparations.

TABLE II

3-ARYLOXY-4-QUINALDINECARBOXYLIC ACIDS



R—	R′—	Yield, %	M. p., °C. (cor.)	Nitrogen, % Calcd.	Nitrogen, % Found
H	*p*-Tolyl	58	206	4.77	4.91
H	*m*-Tolyl	67	224	4.77	4.24
H	*o*-Tolyl	64.8	229	4.77	4.73
CH_3	*p*-Tolyl	72.6	202	4.54	4.42
CH_3	*m*-Tolyl	73.2	231	4.54	4.35
CH_3	*o*-Tolyl	81	225	4.54	4.24
CH_3	α-Naphthyl	40	238	4.08	3.90
CH_3	β-Naphthyl	46.8	233	4.08	3.59

Summary

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

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[1] A part of this paper is taken from the thesis presented to the graduate faculty of the Georgia School of Technology by Arthur M. Dowell, Jr., in partial fulfilment of the requirements for the degree of Master of Science, June, 1947.

[2] Newell and Calaway, THIS JOURNAL, **69**, 116 (1947).

[3] (a) Pfitzinger, *J. prakt. Chem.*, **33**, 100 (1886); (b) **38**, 582 (1888); (c) **56**, 283 (1897).

[4] Stoermer, *Ber.*, **28**, 1253 (1895).

[5] Stoermer, *Ann.*, **312**, 313 (1900).

[6] Calaway and Henze, THIS JOURNAL, **61**, 1355 (1939).

[7] Knight, Porter and Calaway, *ibid.*, **66**, 1893 (1944).

[8] Hurd and Perletz, *ibid.*, **68**, 38 (1946).

2. The naphthoxypropanones have been condensed with 5-methylisatin to produce two substituted quinoline acids.

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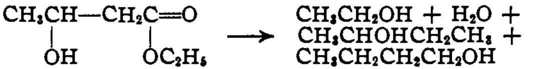
Hydrogenolysis of β-Oxygenated Esters to Glycols

BY RALPH MOZINGO AND KARL FOLKERS

Under the usual conditions for ester reduction,[1] esters containing negative substituents in the β-position to the carboalkoxy group do not give rise to the corresponding alcohols when submitted to hydrogenolysis[2] over copper–chromium oxide catalyst.[3] Under these conditions cleavage products result. However, it has now been found that with these compounds satisfactory ester hydrogenolysis, without additional cleavage at other points, may be accomplished when modified conditions are used.

When ethyl β-hydroxybutyrate is hydrogenated at 250° over copper–chromium oxide under hydrogen at 150–400 atmospheres, the final products obtained are ethyl alcohol, *n*-butyl alcohol and *s*-butyl alcohol,[4] according to the following scheme in which the bonds undergoing hydrogenolysis are indicated by lines.



$$\mathrm{CH_3\underset{|\atop OH}{CH}{-}CH_2\underset{|\atop OC_2H_5}{C}{=}O} \longrightarrow \mathrm{CH_3CH_2OH + H_2O + CH_3CHOHCH_2CH_3 + CH_3CH_2CH_2CH_2OH}$$

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It would appear, however, that the reaction may take the course

$$\mathrm{CH_3CHOHCH_2CO_2C_2H_5} \longrightarrow \mathrm{CH_3CHOHCH_2CH_2OH + C_2H_5OH}$$

$$\mathrm{CH_3CHOHCH_2CH_2OH} \longrightarrow \mathrm{CH_3CHOHCH_2CH_3}\ \textit{or}\ \mathrm{CH_3CH_2CH_2CH_2OH + H_2O}$$

$$\text{or} \longrightarrow 2\mathrm{C_2H_5OH}$$

If the reaction does proceed stepwise and the glycol is not isolated because the second reaction is the more rapid under the conditions which have been used and if sufficiently mild conditions can be found for the hydrogenation, it seems reasonable to expect that some of the glycol might be isolated. Such conditions were found and it was possible to isolate the glycol in reasonable yields.

Since, at any pressure above a certain minimum which is characteristic of the compound being hydrogenated, the effect of temperature is probably the greatest factor in controlling the hydrogenation products, lower temperatures of reaction seemed desirable. It had been demonstrated[5] that the hydrogenation of esters of certain sugar acids at 75° gives rise to the corresponding sugar alcohols. Ethyl α-hydroxyisobutyrate is hydrogenated at 200°.[6] Further, it had been shown that ethyl benzilate is hydrogenated rapidly to the corresponding 1,2-glycol at 125°.[7] In the last case this has been postulated to be due to tautomerization, and the same might be the controlling factor in all of these cases, since each ester contains an α-hydroxyl. The β-hydroxy esters cannot undergo such enolization, but must be hydrogenated in the ester form.

The hydrogenation of β-oxygenated esters was found to proceed smoothly at temperatures between 150 and 180° when relatively large amounts of copper–chromium oxide catalyst[3] were used. The hydrogenation of the β-oxygenated esters appears to be more satisfactory at higher hydrogen pressures (250–400 atmospheres) since the reactions are rather slow. The hydrogenolysis was carried out most successfully in methyl alcohol, which is quite contrary to the general practice when temperatures in excess of 220° are used for ester reduction.[8] For example, ethyl β-hydroxybutyrate (I) (or ethyl acetoacetate)[9] was hydrogenated to 1,3-butylene glycol (II) in 30% yield and ethyl β-ethoxypropionate (III) was converted into 3-ethoxy-1-propanol (IV) in 78% yield.

Likewise, α-alkyl and α-alkylidine acetoacetic esters gave rise to the corresponding 1,3-glycols. Ethyl α-isobutylideneacetoacetate (V) and ethyl ethylacetoacetate (VI) were

$$\underset{\text{I}}{\mathrm{CH_3CHOHCH_2CO_2C_2H_5}} \longrightarrow \underset{\text{II}}{\mathrm{CH_3CHOHCH_2CH_2OH}} + \mathrm{C_2H_5OH}$$

$$\underset{\text{III}}{\mathrm{C_2H_5OCH_2CH_2CO_2C_2H_5}} \longrightarrow \underset{\text{IV}}{\mathrm{C_2H_5OCH_2CH_2CH_2OH}} + \mathrm{C_2H_5OH}$$

converted under these conditions into 2-isobutyl-1,3-butylene glycol (VII) and 2-ethyl-1,3-butylene glycol (VIII), respectively. Both of the racemic forms of these two glycols were formed in the reduction and were separated through their *p*-nitrobenzoyl derivatives.

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(1) Adkins, "Reactions of Hydrogen," University of Wisconsin Press, Madison, Wis., 1937, p. 97.

(2) Connor and Adkins, THIS JOURNAL, **54**, 4678 (1932).

(3) Connor, Folkers and Adkins, *ibid.*, **53**, 2012 (1931).

(4) Adkins, ref. 1, p. 103.

(5) Levene, Meyer and Kuna, *J. Biol. Chem.*, **125**, 703 (1938).

(6) Lazier, U. S. Patent 2,094,611 (October 5, 1937).

(7) Wojcik, Covert and Adkins, THIS JOURNAL, **55**, 1669 (1933).

(8) Lazier, U. S. Patent 2,079,414 (May 4, 1937.)

(9) Since it has been demonstrated that the β-keto esters are converted rapidly to β-hydroxy esters below the temperature used here, the keto esters may be used (see Connor and Adkins, THIS JOURNAL, **53**, 1091 (1931)).