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

Synthesis of 2,3-Disubstituted Cinchoninic Acids from Propoxymethyl Alkyl (or Phenyl) Ketones by Means of the Pfitzinger Reaction[1]

BY HENRY R. HENZE, JOE W. MELTON[2] AND EUGENE O. FORMAN

In 1925 Dilthey and Thelen[3] reported the initial utilization of an alkoxy ketone according to the Pfitzinger method[4] in preparing 3-methoxy-2-phenylcinchoninic acid. More recently, Cross and Henze[5] used this method to convert ethoxyacetone and ethoxymethyl ethyl ketone into the corresponding 2-alkyl-3-ethoxycinchoninic acids. Later, Lesesne and Henze[6] extended this reaction to include the utilization of alkoxy ketones in the synthesis of 2-alkoxyalkyl and 2-alkoxyalkyl-3-alkylcinchoninic acids. Thus, 1-alkoxyethyl methyl ketones appeared to yield cinchoninic acids having the 1-alkoxyethyl grouping attached to the 2-position.

In an attempt to extend the study to a higher homolog of the 1-alkoxyethyl alkyl ketone series, isoamyl 1-methoxyethyl ketone was warmed with isatin under the usual conditions without evidence of reaction. When the attempt was repeated, but using enough alcohol to make the reaction mixture homogeneous, only unsubstituted cinchoninic acid was isolated. Utilization of a 40% aqueous solution of alkali resulted in the formation of a molecular compound of anthranilic acid and 2-(1-methoxyethyl)-3-(2-methylpropyl)-cinchoninic acid.[7]

The availability of certain alkyl (or phenyl) propoxymethyl ketones[8] made it possible to study their behavior with isatin in hot alkaline solution. By this procedure, twelve propoxymethyl ketones were converted into disubstituted cinchoninic acids. The structure of the two heterocyclic compounds derived from the phenyl propoxymethyl ketones was scarcely in doubt. However, their structure was completely established through conversion (by means of decarboxylation and ether group cleavage) into the known 3-hydroxy-2-phenylquinoline.[3]

Confirmation of the structure of this phenylcinchoninic acid did not establish that of the quinoline acids derived from the aliphatic keto ethers, since the latter contain the RCH_2COCH_2OR' grouping which might permit formation of either or both of two isomeric disubstituted cinchoninic acids depending upon which methylene group was involved in the ring closure. It is possible to distinguish between these two isomers by a study of

the products of decarboxylation, of cleavage of the ether linkage, or of both. The cinchoninic acids derived from ethyl isopropoxymethyl ketone and n-propoxymethyl n-propyl ketone, respectively, could be converted into alkali-soluble quinolines, such as the known 2-ethyl-3-hydroxyquinoline.[6] Thus it was established that the hydrogens of the methylene group to which are attached both the ether and carbonyl groupings, are the more reactive in condensation with isatinic acid to form the heterocyclic nucleus
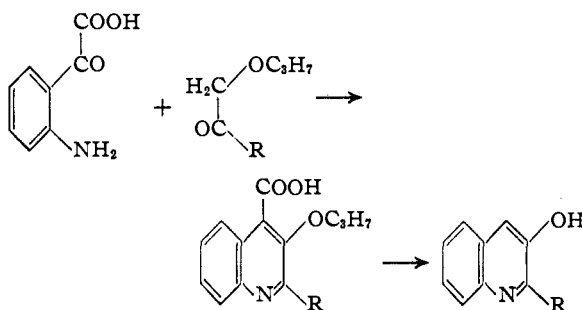
Experimental

The 2,3-disubstituted cinchoninic acids were prepared according to Pfitzinger's procedure by placing 25–50 cc. of 33% potassium hydroxide solution in a small flask and adding equivalent weights of isatin and an alkyl (or phenyl) propoxymethyl ketone. In most cases involving the isopropoxy ketones, enough alcohol was added to render the mixture homogeneous. The mixture was heated for forty-eight hours at about 100°, then was treated (hot) with Norite and filtered. After dilution with water, the filtrate was acidified with 50% acetic acid, usually causing immediate formation of a creamy precipitate. If necessary the acid solution was chilled before separation of the crystalline product. Each acid was purified by recrystallization to constant melting point from diluted alcohol or acetone. Only the purified products could be dried without decomposition in an oven. Data for the melting points and analyses of these acids are listed in Table I.

Proof of Structure of 2-Phenyl-3-propoxycinchoninic Acid.—This product, obtained through interaction of isatin and phenyl n-propoxymethyl ketone, was placed together with 15 cc. of concentrated hydrochloric acid in a sealed tube and heated at 175° for twelve hours. After opening the tube, the mixture was neutralized with sodium bicarbonate, and the substituted quinoline removed by filtration and recrystallized from an acetone-water solution. The melting point of the alkali soluble 3-hydroxy-2-phenylquinoline (228° (cor.)) is somewhat higher than that (218–220°) reported by Dilthey and Thelen[3] for this product.

Anal. Calcd. for $C_{15}H_{11}NO$: C, 81.43; H, 5.01; N, 6.33. Found: C, 81.31; H, 4.89; N, 6.49.

One-half gram of the hydroxyquinoline derivative was dissolved in 75 cc. of alcohol and treated with 40 cc. of saturated aqueous picric acid solution. A picrate soon

(1) From the M. A. theses of J. W. M. (Aug., 1940) and E. O. F. (June, 1941).

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(3) Dilthey and Thelen, *Ber.*, **58**, 1588 (1925).

(4) Pfitzinger, *J. prakt. Chem.*, **33**, 100 (1886); **38**, 582 (1888); **56**, 283 (1897).

(5) Cross with Henze, THIS JOURNAL, **61**, 2730 (1939).

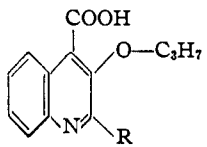(6) Lesesne with Henze, *ibid.*, **64**, 1897 (1942).

(7) Isbell with Henze, *ibid.*, **66**, 2096 (1944).

(8) Henze, Duff, Matthews, Melton and Forman, *ibid.*, **64**, 1222 (1942).

(9) Cross with Henze, see ref. 5, p. 2731.

<div align="center">TABLE I</div>

PHYSICAL AND ANALYTICAL DATA FOR 2,3-DISUBSTITUTED CINCHONINIC ACIDS

COOH
O—C₃H₇
N   R

(structure: COOH, $\text{O—C}_3\text{H}_7$ substituted quinoline with R)

C₃H₇–	R	Yield, %	M. p., °C.	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Nitrogen, % Calcd.	Found
n	—CH₂CH₃	64	187.0	69.48	69.66	6.61	6.48	5.40	5.40
iso-	—CH₂CH₃	20	197.0	69.48	69.33	6.61	6.63	5.40	5.50
n-	—(CH₂)₂CH₃	56	157.0	70.31	70.39	7.01	6.81	5.13	5.32
iso-	—(CH₂)₂CH₃	42	120.5	70.31	70.07	7.01	7.16	5.13	5.20
n-	—(CH₂)₃CH₃	55	123.0	71.05	71.63	7.37	7.28	4.88	5.25
iso-	—(CH₂)₃CH₃	41	104.6	71.05	70.74	7.37	7.25	4.88	4.75
iso-	—CH₂CH(CH₃)₂	50	163.7	71.05	70.64	7.37	7.52	4.88	4.98
iso-	—(CH₂)₄CH₃	32	68.3	71.73	71.55	7.69	7.89	4.65	4.74
n-	—(CH₂)₂CH(CH₃)₂	53	129.0	71.73	71.73	7.69	7.61	4.65	4.66
iso-	—(CH₂)₂CH(CH₃)₂	43	110.0	71.73	70.13	7.69	7.88	4.65	4.63
n-	—C₆H₅	48	216.0	74.25	74.27	5.58	5.45	4.56	4.78
iso-	—C₆H₅	59	210.0	74.25	74.07	5.58	5.49	4.56	4.596

separated and was recrystallized from alcohol; it melted[10] with decomposition at 245° (cor.).

Anal. Calcd. for $C_{21}H_{14}N_4O_8$: N, 12.44. Found: N, 12.59.

Proof of Structure of 3-(n-Propoxy)-2-(n-propyl)-cinchoninic Acid.—One gram of the product from interaction of isatin and n-propyl n-propoxymethyl ketone was dissolved in 15 cc. of concentrated hydrochloric acid, sealed in a tube and heated at 165° for twelve hours. When cooled, solid material separated from solution and, after drying in the oven at 110°, melted at 223° (cor.). This proved to be the hydrochloride of a substituted quinoline. It was dissolved in water and decomposed by addition of sodium bicarbonate; the liberated quinoline was recrystallized from an acetone–water mixture. The product, 3-hydroxy-2-n-propylquinoline, melts at 256° (cor.), and is readily soluble in alkaline solution.

Anal. Calcd. for $C_{12}H_{13}NO$: N, 7.48. Found: N, 7.91.

A small amount of this disubstituted quinoline was dissolved in 95% alcohol, and mixed with 10 cc. of saturated aqueous solution of picric acid. After chilling the *picrate* separated as long crystals melting with decomposition at 158° (cor.).

Anal. Calcd. for $C_{18}H_{16}N_4O_8$: N, 13.46. Found: N, 13.73.

Proof of Structure of 2-Ethyl-3-isopropoxycinchoninic Acid.—Three methods were used in the conversion of this acid into 2-ethyl-3-hydroxyquinoline.

A. A mixture of 1.5 g. of 2-ethyl-3-isopropoxycinchoninic acid and 15 cc. of concentrated hydrochloric acid was sealed in a tube and heated at 175° for twelve hours. Upon dilution of the resulting solution with water, a white precipitate formed and was purified by solution in dilute sodium hydroxide solution with subsequent reprecipitation with dilute acetic acid solution. After recrystallization from acetone, the solid melted with decomposition at 205.5–208.0° (cor.).[11]

B. A sample of 2-ethyl-3-isopropoxycinchoninic acid was decarboxylated by heating to its melting point of 197°. The dark oil thus formed was distilled at 209–214° (42 mm.): 78% yield of 2-ethyl-3-isopropoxyquinoline. This material was sealed in a tube with concd. hydrochloric acid and heated to 200° for five hours. After diluting the solution with water, creamy white crystals separated and were purified as above; m. p. 205–208°.

(10) Bargellini and Berlingozzi, *Gazz. chim. ital.*, **53**, 3 (1923), reported m. p. 235–238° (dec.).

(11) Cross with Henze, ref. 5, reported m. p. 206–208° (cor.)(dec.).

Anal. Calcd. for $C_{11}H_{11}NO$: N, 8.07. Found: N, 8.22.

C. A mixture of 2 g. of 2-ethyl-3-isopropoxycinchoninic acid, 15 cc. of hydriodic acid and 1.25 g. of red phosphorus was refluxed for twenty-four hours. The hot mixture was filtered through asbestos and cooled to yield a yellow precipitate. The latter was filtered off, dissolved in sodium hydroxide solution and precipitated by addition of acetic acid. The solid was recrystallized to a constant m. p. of 206–207° (cor.) from alcohol and water.

Anal. Calcd. for $C_{11}H_{11}NO$: N, 8.07. Found: N, 8.27.

The yellow acidic filtrate from above was steam distilled and the residual solution concentrated by evaporation to 25 cc. It was neutralized with dilute sodium hydroxide solution; the yellow precipitate which first formed was redissolved in excess alkaline solution and reprecipitated with dilute acetic acid. The purified material melted at 179–182° with evolution of a gas and re-fused at 206–208° (cor.).[12]

Preparation of Picrates.—Certain of the cinchoninic acids were decarboxylated by being heated at a temperature approximately 40° above their melting points. After decarboxylation seemed complete, the resin was subjected to distillation under diminished pressure; about 90% of the theoretical yield of quinoline could be obtained. The quinoline was dissolved in alcohol and treated with a saturated solution of picric acid, which usually resulted in the immediate separation of the solid picrate. Re-

<div align="center">TABLE II</div>

PICRATES OF CERTAIN 2-SUBSTITUTED-3-n-PROPOXY-QUINOLINES

Alkyl-	M. p., °C.	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Nitrogen, % Calcd.	Found
Ethyl	203	54.05	53.81	4.54	4.34	12.64	12.73
n-Propyl	191	55.02	54.83	4.84	4.67	12.22	12.41
n-Butyl	175	55.93	55.79	5.12	5.11	11.86	11.84
Isoamyl	198	56.78	56.66	5.36	5.21	11.52	11.67
Phenyl	206	58.53	58.24	4.09	3.97	11.38	11.65
Phenyl[a]	210	58.53	58.35	4.09	4.24	11.38	11.53

[a] Represents the picrate of 2-phenyl-3-isopropoxy-quinoline.

(12) Cross with Henze, ref. 5, page 2732, reported m. p. of 2-ethyl-3-hydroxycinchoninic acid as 208–209° (dec.); the m. p. was noted after introducing the sample into the bath heated to about 200°. When warmed from room temperature at the usual rate, this material softens with evolution of gas at 179–181° (cor.) and melts at 206–208° (cor.).

crystallization was effected from alcohol. The melting points of the picrates were sharp with decomposition occurring only after fusion was complete. Data for the picrates are collected in Table II.

Summary

Twelve new 2,3-disubstituted cinchoninic acids have been prepared from alkyl (or phenyl) pro-poxymethyl ketones. Certain of these derivatives have been decarboxylated and their ether grouping cleaved to produce 2-alkyl (or 2-phenyl)-3-hydroxyquinolines, thus establishing the structures as 2-alkyl (or 2-phenyl)-3-propoxycinchoninic acids.
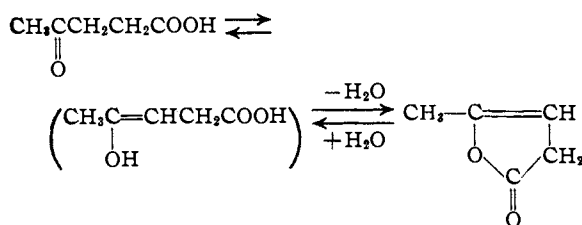

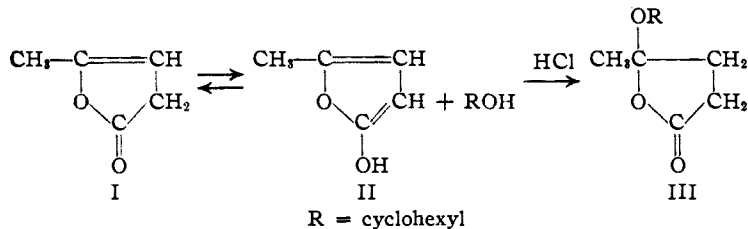# Pseudo Esters of Levulinic Acid

BY DAVID P. LANGLOIS AND HANS WOLFF

The dehydration of levulinic acid to α-angelica lactone is a reversible reaction. In the presence of traces of mineral acids water can be added to α-angelica lactone re-forming levulinic acid.[1] The enolic form of levulinic acid may be an intermediate in the reaction

$$CH_3CCH_2CH_2COOH \rightleftarrows$$
$$\underset{O}{\|}$$

$$\left(\underset{\underset{OH}{|}}{CH_3C{=}CHCH_2COOH} \right) \underset{+H_2O}{\overset{-H_2O}{\rightleftarrows}} \underset{O}{\underset{\underset{O}{\|}}{\overset{}{CH_3{-}\underset{\diagdown_{C}\diagup}{C}{=}\underset{CH_2}{\overset{CH}{}}}}}$$

If instead of water an alcohol is added to α-angelica lactone, the corresponding ester of levulinic acid would be expected as the reaction product. With the intention of preparing levulinic esters by this method, methanol and ethanol were added to α-angelica lactone in the presence of hydrogen chloride. The corresponding methyl and ethyl esters were obtained in quantitative yields.

Attempts to prepare cyclohexyl levulinate by this same method led to an unexpected result; an ester was obtained in 95% yield, but its physical and chemical properties differed from cyclohexyl levulinate prepared from levulinic acid and cyclohexanol by conventional methods. A further ex-

$$\underset{I}{\underset{O}{\underset{\|}{}}\overset{}{CH_3{-}\underset{\diagdown_{C}\diagup}{C}{=}\underset{CH_2}{\overset{CH}{}}}} \rightleftarrows \underset{II}{\underset{OH}{\underset{|}{}}\overset{}{CH_3{-}\underset{\diagdown_{C}\diagup}{C}{=}\underset{CH}{\overset{CH}{}}}} + ROH \longrightarrow \underset{III}{\underset{O}{\underset{\|}{}}\overset{OR}{\underset{\diagdown_{C}\diagup}{CH_3C}{\underset{}{}}\underset{CH_2}{\overset{CH_2}{}}}}$$

R = cyclohexyl

amination of the product revealed that it consisted predominately of the pseudo cyclohexyl ester of levulinic acid (III), which could result either from the addition of cyclohexanol to the double bond of α-angelica lactone (I) or from a 1–4 addition of the alcohol to the enol form of angelica lactone (II) followed by rearrangement to structure (III).

The presence of an enol form of α-angelica lactone is indicated by a Zerewitinoff determination in which approximately one third of a mole of methane is liberated from one mole of α-angelica lactone. Additional evidence for an enol form is given by a comparison of the ultraviolet absorption spectra of furfuryl alcohol and α-angelica lactone (Fig. 1). Furfuryl alcohol was chosen for comparison because it possesses the same molecular weight as angelica lactone and has a structure quite similar to the enol form of α-angelica lactone. The maximum of absorption at 2170 Å., indicative of two double bonds in conjugation, is common to both compounds; the considerably lower absorption of the lactone would indicate that only a partial enolization occurs.

Pseudo esters of aromatic keto acids have been described. Meyer[2] prepared pseudo methyl 2-benzoylbenzoate; Lutz[3] reported the pseudo esters of substituted benzoylacrylic acid and Newman[4] discussed the synthesis of pseudo esters of the benzoylbenzoic acid type. It appears that the pseudo esters of levulinic acid described in this paper are the first examples of pseudo esters in the purely aliphatic series.

In studying the various alcohols it was observed that secondary alcohols form pseudo esters quite readily. This is also true in the case of reactive primary alcohols such as allyl and benzyl alcohols. On the other hand, normal primary alcohols, especially the lower members, give only the normal esters of levulinic acid unless special precautions are taken. The pseudo ester of methanol can be obtained, however, if ether is used as a solvent and the quantity of hydrogen chloride is regulated carefully.

The rate of reaction for each alcohol is controlled by the amount of catalyst used. The reaction is exceedingly violent if a large excess of hydrogen chloride is added at the start, and

(1) Wolff, Ann., 229, 249 (1885).

(2) Meyer, Monatsh, 25, 475 (1904).

(3) Lutz and Winne, THIS JOURNAL, 56, 445 (1934); Lutz, ibid., 56, 1378 (1934); Lutz, et al., J. Org. Chem., 4, 95 (1939); 6, 77 and 91 (1941).

(4) Newman and McClearly, THIS JOURNAL, 63, 1537 (1941); Newman and Lord, ibid., 66, 731 (1944).