A sample of cut 2 (12.5 g.) was dehydrogenated over platinum on charcoal at 350° and yielded 8.45 l. of hydrogen (theoretical = 8.5 l. assuming 5 moles per mole of sample). The dehydrogenated material (9.7 g.) was then distilled.

Cut	B.p., °C.	Vol., cc.	$n^{25}D$
1	210–236	0.8	1.5381
2	236–258	2.4	1.5934
3	258–263	2.2	1.6045
4	263–268	1.8	1.6053
	Residue	2.3	1.6072

The boiling point and refractive index values agree with the literature[14] values for the liquid dimethylnaphthalene isomers (b.p. 263–266°, $n^{20}D$ 1.6072–1.6164).

White crystals separated from cuts 3, 4 and residue. Cut 4 was filtered and the solid recrystallized from ethanol yielding white plates, m.p. 110–110.5°. The picrate was prepared and found to melt at 141–142°. These values check the literature[14] values of 2,6-dimethylnaphthalene.

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[14] A. S. Bailey, K. C. Bryant, R. A. Hancock, S. H. Morrell and J. C. Smith, *J. Inst. Pet.*, **33**, 503 (1947).

NORWOOD, PENNA.

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

Utilization of *n*-Alkyl Methyl Ketones in the Pfitzinger Reaction[1]

BY HENRY R. HENZE AND DONALD W. CARROLL[2]

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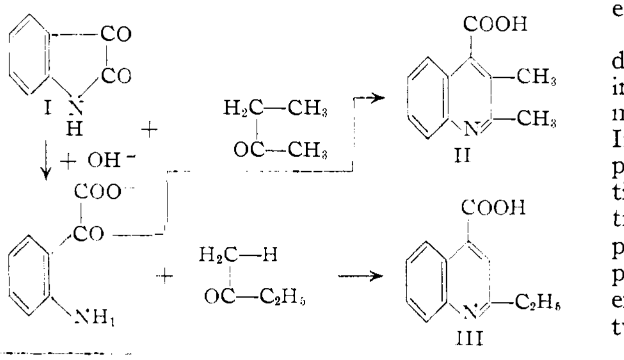
A series of Pfitzinger condensations, utilizing *n*-alkyl methyl ketones (alkyl = methyl through hexyl), has been accomplished. The unsymmetrical ketones produce two isomeric cinchoninic acids, a 2-monosubstituted acid and a 2,3-disubstituted acid, the monosubstituted compound usually being formed in the larger amount. A new sequence of syntheses has been developed in order to establish the structure of one series of these isomeric cinchoninic acids.

Although the Pfitzinger reaction[3] is one of the more commonly used procedures for preparation of quinoline derivatives,[4–6] surprisingly little attention has been given to the study of the structure of the products resulting from the utilization in this synthesis of mixed aliphatic ketones of the type RCH_2COCH_2R'. Since this synthesis in part involves condensation of the β-carbonyl group in isatin with a methylene group adjacent to the carbonyl group of the ketone, obviously two isomeric products should be capable of formation from this unsymmetrical ketone type, RCH_2COCH_2R'. From the initial condensation of ethyl methyl ketone with isatin (I), Pfitzinger[3] reported only the isolation of 2,3-dimethylcinchoninic acid (II). However, subsequently v. Braun, *et al.*,[7] showed that a smaller amount of the isomeric 2-ethylcinchoninic acid (III) was produced also. From the meager experimental data then available, Hollins[8] stated that the course of reaction in the Pfitzinger synthesis is such that "as in the Friedländer synthesis, the quinolines from unsymmetrical ketones usually contain the *smaller* group in the α-position." A survey of the literature fails to disclose a sufficient number of condensations either to substantiate or to refute Hollins' statement.



More recently, Buu-Hoï, *et al.*,[9] have made a partial study of this condensation, utilizing the ethyl, propyl, hexyl and nonyl homologs of acetone; data reflecting these and a few other pertinent condensations have been collected in Table I. Buu-Hoï concluded that the condensation of isatin with *n*-alkyl methyl ketones, excluding ethyl methyl ketone, yielded primarily 2-monosubstituted cinchoninic acids. However, this conclusion was not based upon isolation of two products from each of the condensations studied.

In the present investigation, isatin has been condensed, under the condition typical for the Pfitzinger reaction, with five members of the *n*-alkyl methyl ketone series, namely, ethyl through hexyl. In each instance, evidence was obtained of the production of two reaction products. After separation of the products, through fractional crystallization of the reaction product, the isomeric compounds were mixed in known amounts and melting point studies made of the known mixtures in an effort to evaluate the relative amounts formed of the two isomers in a given condensation.

In the case of the condensation of isatin with ethyl methyl ketone, the two isomers were obtained; in all probability, five-sixths of the mixture of isomers was made up of the 2,3-disubstituted cinchoninic acid. The identity of the lesser prod-

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[1] From the Ph.D. dissertation of Donald Wesley Carroll, The University of Texas, June, 1952.

[2] Research Scientist I, University of Texas Research Institute, 1952 Summer Session.

[3] W. Pfitzinger, *J. prakt. Chem.*, [2] **33**, 100 (1886); **38**, 583 (1888); **56**, 283 (1897).

[4] C. Hollins, "The Synthesis of Nitrogen Ring Compounds," E. Benn, Ltd., London, 1924, Chapter VIII.

[5] A. A. Morton, "The Chemistry of Heterocyclic Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1946, p. 273.

[6] R. C. Elderfield, "Heterocyclic Compounds," Vol. 4, John Wiley and Sons, Inc., New York, N. Y., 1952, p. 54.

[7] J. v. Braun, W. Gmelin and A. Schultheiss, *Ber.*, **56**, 1338 (1923).

[8] J. Hollins, ref. 4, p. 287; with regard to the Friedländer synthesis Hollins wrote (p. 284) "In the case of ketones of the type $MeCO\cdot CH_2R$, the methyl group takes the α-position in the resulting quinoline."

[9] Ng. Ph. Buu-Hoï, *J. Chem. Soc.*, 795 (1946); Buu-Hoï and P. Cagniant, *Bull. soc. chim.*, 13 (1946); Buu-Hoï and R. Royer, *ibid.*, 374 (1948). See also Ng. Ph. Buu-Hoï, R. Royer, Ng. D. Xuong and P. Jacquignon, *J. Org. Chem.*, **18**, 1209 (1953).

TABLE I

CINCHONINIC ACIDS, FORMED IN PFITZINGER CONDENSATION, FROM KETONES OF TYPE FORMULA RCOR′

Ketone, RCOR′		Cinchoninic acid substituents		
R	R′	Major product	Minor product	References
Methyl	Methyl	2-Methyl		[a]
Methyl	Ethyl	2,3-Dimethyl	2-Ethyl	[b,c]
Methyl	Propyl	2-Propyl	Not isolated	[c]
Methyl	Amyl	2-Amyl	Not isolated	[d]
Methyl	Hexyl	2-Hexyl	Not isolated	[c]
Methyl	Nonyl	2-Nonyl	Not isolated	[c]
Methyl	Benzyl	2-Methyl, 3-phenyl	2-Benzyl	[e] [e]
Methyl	β-Phenylethyl	2-β-Phenylethyl	Not characterized	
Ethyl	Benzyl	2-Ethyl, 3-phenyl	2-Benzyl, 3-methyl	[e,f]

[a] W. Pfitzinger, *J. prakt. Chem.*, (2) **33**, 100 (1886). [b] J. v. Braun, *et al.*, *Ber.*, **56**, 1345 (1923). [c] Ng. Ph. Buu-Hoï and R. Royer, *J. Chem. Soc.*, 106 (1948). From this condensation Buu-Hoï and Royer reported recovery of 2,3-dimethylcinchoninic acid, but did not disclose any efforts toward the isolation of the isomeric 2-ethylcinchoninic acid. Elderfield [ref. 6, p. 54], cites this work in contrast to that of v. Braun and co-workers (see reference *b* above), who effected a separation of the two isomers from the condensation, and states, ". . .Buu-Hoï reports that methyl ethyl ketone condenses with isatic acid to yield 2,3-dimethylcinchoninic acid exclusively, from which it is concluded that condensation occurs only through the methylene group of the methyl ethyl ketone." A review of the report by Buu-Hoï and Royer vitiates the interpretation laid upon it by the above author. [d] W. Salzer, *et al.*, *Ber.*, **81**, 12 (1948). [e] W. Borsche and O. Vorbach, *Ann.*, **537**, 22 (1939). [f] G. B. Crippa and E. Sçevola, *Gazz. chim. ital.*, **67**, 119 (1937).

uct, 2-ethylcinchoninic acid, was confirmed through independent synthesis using the Döbner modification[10] of the Skraup synthesis. In the case of condensation using ethyl methyl ketone, the methylene group chiefly is involved. However, although the condensation of isatin with the mixed methyl ketones containing five, six, seven and eight carbon atoms, led also to production of mixtures of two isomeric cinchoninic acids, now the chief product in each case was the 2-monosubstituted cinchoninic acid resulting from utilization of the methyl grouping.

Although the oxidation of 2-alkylcinchoninic acid to the known 2,3-quinolinedicarboxylic acid offers a possibility of establishing the formation of a pyridine tetracarboxylic acid, such a degradation does not serve to distinguish between two acids differently substituted in the 2,3-positions. Therefore, an alternate route was developed for the unambiguous synthesis of 3-alkyl-2-methylcinchonic acids. This procedure involves synthesis of a γ,γ-dialkoxyacetoacetic ester, alkylation of the latter, and subsequent decarboxylation to yield an alkyl dialkoxymethyl ketone. Upon condensation of the latter with isatin, only one cinchoninic acid derivative results, since the mixed ketone contains but one active methylene group. Cleavage and reduction of the 3-alkyl-2-dialkoxymethylcinchoninic acid leads to production of the 3-alkyl-2-methyl analog. In this manner, 3-ethyl-2-methylcinchoninic acid and 3-butyl-2-methylcinchoninic acid were prepared.

The behavior of 3-ethyl-2-formylcinchoninic acid toward the reducing action of amalgamated zinc and hydrochloric acid was unexpected, in that partial decarboxylation of the anticipated reduction product occurred. Further study indicated that the phenomenon of decarboxylation in acid medium occurred only for the 2,3-disubstituted cinchoninic acids and that the presence of the amalgamated zinc was necessary to cause this alteration.

The determination of the ultraviolet absorption spectra for these cinchoninic acids was undertaken to ascertain whether the size and/or the position of the alkyl substituents in the cinchoninic acid nucleus would characteristically alter the fundamental absorption spectrum of the parent compound. It was found that substitution of the alkyl groups into the 2- or 3- or 2,3-positions did not significantly change the maximum or minimum points of absorption. On the other hand, the 2-formylcinchoninic acids were observed to cause such a change, evidently due to the formyl group which introduced a point of unsaturation in conjugation with the fundamental absorbing system of conjugated double bonds.

An X-ray diffraction pattern study was undertaken to determine whether there was any constant difference in the patterns for four pairs of isomeric cinchoninic acids and whether any graduated change in the patterns accrued for the series of homologous compounds. A study of the *d*-spacing values for these compounds showed that no generalizations along these lines could be drawn. Thus the X-ray diffraction pattern of known cinchoninic acids can be utilized to identify which of a pair of isomeric compounds is formed in larger amount from condensation of a mixed ketone with isatin in the Pfitzinger reaction.

Experimental

Condensation of Isatin with Ethyl Methyl Ketone.—A mixture of 60 g. (0.408 mole) of isatin, 200 ml. of 34% potassium hydroxide in diluted alcohol solution, 88 g. (1.22 moles) of ethyl methyl ketone and 375 ml. of water was stirred and heated under reflux for 72 hours. About 125 ml. of liquid was removed by distillation; the residue was made faintly acidic and filtered. The filtrate was acidified strongly to precipitate the reaction product; the latter after being filtered off, washed and dried, weighed 70 g. (85% yield). After recrystallization, the mixture began sintering at 248° and finally decomposed above 300°. Repeated recrystallizations from water,[11] and from dilute alcohol yielded the higher melting component, **2,3-dimethylcinchoninic acid** (m.p., with rapid decomposition, above 320°).

Preparation of 2-Ethylcinchoninic Acid.—In order to obtain this compound in a purer condition than that afforded through recrystallization of the by-product from the Pfitzinger reaction, 2-ethylcinchoninic acid was prepared by adding to a solution of 25 g. (0.28 mole) of pyruvic acid and 17 g. (0.29 mole) of propionaldehyde in 100 ml. of ethyl alcohol, over a period of 1.5 hours, a solution of 27 g. (0.29 mole) of aniline in 50 ml. of alcohol, the temperature being maintained at about 5°. The mixture was warmed gently for 3 hours and then refluxed for 7 hours longer. The solution was concentrated to about 110 ml. and upon cooling in an ice-bath there separated a yellow solid which was purified by treatment with alcohol and acetone; wt. 4.5 g. (10% yield), m.p. 180–181°.[12]

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(10) O. Döbner, *Ann.*, **242**, 265 (1887).

(11) In this investigation, it appeared that the 2,3-disubstituted cinchoninic acids were more soluble than the 2-monosubstituted cinchoninic acids in polar solvents, whereas just the reverse was true of their solubilities in non-polar solvents. There is no clear indication that this difference in behavior is related to the acid strengths of these compounds. Samples of 2,3-dimethylcinchoninic acid and its isomer, 2-ethylcinchoninic acid, were titrated with the aid of a Beckman *p*H meter; the *p*H (8.2) at neutralization was identical for both acids.

(12) S. Lesesne and H. R. Henze, THIS JOURNAL, **64**, 1889 (1942), reported m.p. 180°; O. Döbner, ref. 10, reported m.p. 173° for the dihydrate of this acid.

The m.p. behavior for a series of known mixtures of purified 2,3-dimethyl- and 3-ethylcinchoninic acids was determined. From a plot of such data, it was estimated that approximately 85% of the reaction product from condensation of isatin and ethyl methyl ketone was 2,3-dimethylcinchoninic acid.

Condensation of Isatin and Methyl Propyl Ketone.—Sixty grams (0.408 mole) of isatin, 120 g. (1.4 moles) of methyl propyl ketone, 200 ml. of the 34% potash solution and 370 ml. of water were stirred and heated under reflux for 72 hours. After the usual preliminary treatment, there was obtained 81 g. (92% yield) of mixed acids having a wide range in m.p. beginning at 131°. When purified, the major product, 2-propylcinchoninic acid[13] (silvery white platelets) melted with some decomposition at 159.0–159.5°.

By repeated recrystallization of 30 g. of the reaction product, there was obtained 7 g. of material which melted above 220°. This compound, **3-ethyl-2-methylcinchoninic acid,** was shown to constitute about 20–25% of the condensation product by plotting the m.p. behavior of known mixtures of the purified pair of isomers. The disubstituted acid was recrystallized from dioxane as a white, friable powder melting with decomposition at 257–258°.[14]

Anal. Calcd. for $C_{13}H_{13}NO_2$: neut. equiv., 215.2; C, 72.52; H, 6.09; N, 6.51. Found: neut. equiv., 218.1; C, 72.30; H, 6.03; N, 6.88.

This acid was heated to effect decarboxylation to form **3-ethyl-2-methylquinoline** which yielded a **picrate** melting with decomposition at 227–230°.

Anal. Calcd. for $C_{18}H_{16}N_4O_7$: C, 53.98; H, 4.02; N, 14.03. Found: C, 53.65; H, 4.18; N, 14.29.

Condensation of Isatin and Butyl Methyl Ketone.—A solution containing 60 g. (0.408 mole) of isatin, 108 g. (1.08 moles) of butyl methyl ketone, 200 ml. of the 34% potash solution and 375 ml. of water was stirred and heated for 70 hours. The reaction product weighed 119 g. (93% yield) and began to melt at about 121°. After extensive recrystallizations, the chief product, **2-butylcinchoninic acid,** was secured as a white, friable powder or very fine leaflets melting without apparent decomposition at 141–142°.

Anal. Calcd. for $C_{14}H_{15}NO_2$: neut. equiv., 229.2; C, 73.33; H, 6.60; N, 6.12. Found: neut. equiv., 232; C, (74.00); H, 6.65; N, 5.85.

Decarboxylation of this acid to its corresponding quinoline was effected and the picrate of 2-butylquinoline was prepared. Repeated preparation of this picrate verified its melting without decomposition at 162°.[15]

Anal. Calcd. for $C_{19}H_{17}N_4O_7$: N, 13.53. Found: N, 13.83.

The isomeric **2-methyl-3-propylcinchoninic acid** was isolated in small amount with difficulty through fractional extraction of the reaction product. The acid separated from dioxane as a snow-white powder which melted with extensive decomposition above 290°.

Anal. Calcd. for $C_{14}H_{15}NO_2$: neut. equiv., 229.2; N, 6.12. Found: neut. equiv., 233.6; N, 6.51.

This isomer composed 10–12% of the reaction product, as indicated by the melting point data of quantitative mixtures of the pure acids.

Condensation of Isatin and Amyl Methyl Ketone.—A solution of 60 g. (0.408 mole) of isatin, 105 g. (0.925 mole) of amyl methyl ketone, 400 ml. of 34% potash solution and 900 ml. of water was stirred and refluxed for 78 hours. The reaction product weighed 79 g. (80% yield) and melted over a range beginning about 125°. After repeated recrystallization, the chief product, **2-amylcinchoninic acid,** melted with slight decomposition at 135–136°.[16]

Anal. Calcd. for $C_{15}H_{17}NO_2$: neut. equiv., 243.2. Found: neut. equiv., 246.8.

The 2-amylcinchoninic acid was decarboxylated and the resulting quinoline yielded the known picrate of 2-amylquinoline. This picrate melted without apparent decomposition at 103.0–103.5° and recrystallization from diluted alcohol did not raise the m.p. of the fine yellow crystals.[17]

The minor product formed in this condensation, **3-butyl-2-methylcinchoninic acid,** could be isolated through treatment of the reaction product with hot dioxane (which left the disubstituted acid largely undissolved). Crystallized from alcohol, the granular white powder melted with decomposition at 261–263°.

Anal. Calcd. for $C_{15}H_{17}NO_2$: neut. equiv., 243.2; C, 74.04; H, 6.99; N, 5.75. Found: neut. equiv., 247; C, 74.37; H, 6.95; N, 5.60.

A study of the m.p. data of known mixtures of these two isomeric acids indicated that 3-butyl-2-methylcinchoninic acid constituted only about 5% of the reaction product mixture. A small amount of this acid was decarboxylated to form **3-butyl-2-methylquinoline** which yielded a **picrate;** fine yellow needles melting with decomposition at 210–212°.

Anal. Calcd. for $C_{20}H_{20}N_4O_7$: N, 13.08. Found: N, 12.97.

Condensation of Isatin and Hexyl Methyl Ketone.—The solution of 50 g. (0.34 mole) of isatin and 75 g. (0.58 mole) of hexyl methyl ketone in 180 ml. of the 34% potash solution and 300 ml. of water was stirred and refluxed for 96 hours. The reaction product weighed 82 g. (92% yield) and after recrystallization from water melted at 136–140°. Repeated recrystallization from methanol yielded silvery platelets of 2-hexylcinchoninic acid melting without apparent decomposition at 140–141°.[18] The acid was decarboxylated and the picrate of the resulting quinoline was obtained with difficulty by action of methanolic solution of picric acid. This picrate melted with decomposition at 110–112°

The isomeric compound, 2-amyl-2-methylcinchoninic acid, although possibly present in the small amount of by-product from this condensation, was not isolated in this investigation despite carefully considered efforts to do so.

Oxidation of 2-Methylcinchoninic Acid.—Eight grams of 2-methylcinchoninic acid[19] was dissolved in 200 ml. of water containing 2 g. of sodium hydroxide. This solution was kept hot on a steam-cone and was stirred while a solution of 67 g. of potassium permanganate in 1200 ml. of water was added dropwise during a period of 7 hours. Immediate decomposition of manganese dioxide was noted, but the mixture was heated for 70 hours before a few milliliters of alcohol was added to destroy the excess permanganate. After filtration, the clear filtrate was evaporated to about 500 ml., acidified with nitric acid and treated with 200 ml. of a hot solution of copper acetate (17 g.). A pasty, blue precipitate formed, was filtered off and washed on the filter with about 500 ml. of molar acetic acid. The solid was transferred to 450 ml. of water and stirred while the mixture was saturated with hydrogen sulfide. Copper sulfide formed and was removed, the filtrate being evaporated to dryness. The residue, about 2 g., when extracted with hot methanol yielded a purplish gel which set to a solid (1.5 g.). This material was pulverized and extracted in a Soxhlet apparatus with ethyl acetate. Evaporation of the solvent left a light tan solid, which melted at 182–184° and expanded to resolidify and then fuse with extensive decomposition at about 223–227°.[20] A neutralization equivalent of 73.7 compared favorably with the value 72.8 based on $C_5NH(COOH)_4 \cdot 2H_2O$. Thus, the m.p. and neutralization equiva-

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[13] Buu-Hoï and R. Royer, ref. 9, reported m.p. 156°, while J. A. J. Tonella, *Rec. trav. chim.*, **16**, 361 (1897), listed 152.5° as the m.p. of the dihydrate of this acid.

[14] This 3-ethyl-2-methylcinchoninic acid was not isolated by Buu-Hoï and Royer, ref. 9, from a similar condensation.

[15] R. Delaby and J. Hiron, *Bull. soc. chim.*, [4] **47**, 1399 (1930), reported m.p. 143°.

[16] This condensation was previously reported by W. Salzer, H. Timmler and H. Andersag, *Ber.*, **81**, 12 (1948), who ascribed this m.p. of 136° dec. to 3-butyl-2-methylcinchoninic acid, the isomer actually formed in very small yield, and which has been found herein to melt at 261–263° dec.

[17] T. Taylor and P. Hobson, *J. Chem. Soc.*, 181 (1936), reported m.p. 104–105° and a correct analysis for nitrogen content in this picrate, whereas C. Schopf and G. Lehmann, *Ann.*, **497**, 7 (1932), listed m.p. 110–111°.

[18] Buu-Hoï and R. Royer, ref. 9, reported a homogeneous reaction product from this condensation; m.p. 139–140°. They also reported decarboxylation to a quinoline which gave a picrate melting at 112°.

[19] Prepared *via* the usual Pfitzinger condensation of isatin and acetone.

[20] O. Fischer and E. Täuber, *Ber.*, **17**, 2925 (1884), reported m.p. 187° for a hydrated form of this acid, and 227° dec. for the anhydrous form. R. Michael, *Ann.*, **225**, 121 (1884), demonstrated that the acid was obtained initially as a dihydrate, and listed 188° for its m.p.

lent indicated that this oxidation product of 2-methylcinchoninic acid was 2,3,4,6-pyridinetetracarboxylic acid.

Preparation of Ethyl γ,γ-Diethoxy-α-ethylacetoacetate.—To a solution of 4.8 g. (0.206 g.-atom) of sodium in 100 ml. of ethanol was added 45 g. (0.206 mole) of ethyl γ,γ-diethoxyacetoacetate.[21] While the solution was stirred at the temperature of reflux over a period of 70 minutes, there was added 26 g. (0.24 mole) of ethyl bromide and the mixture was refluxed for 13 hours. The slightly orange liquid was filtered from the sodium bromide, diluted with water, and the ester extracted with ether and dried with sodium sulfate. After fractionation, there was obtained 38.5 g. (76% yield) of the ester boiling at 118–121° (5 mm.). When treated with ferric chloride solution, this colorless ester yielded a deep amber color within one minute. For the ester was found: n^{20}_{D} 1.4270, d^{20}_{20} 1.0085, Σ *MR* (keto form) 62.57, Σ *MR* (enol form) 63.61, *MR* calcd. 62.72.

Anal. Calcd. for $C_{12}H_{22}O_5$: C, 58.52; H, 8.98. Found: C, 58.40; H, 8.94.

Preparation of 1,1-Diethoxy-2-pentanone.—A mixture of 35.5 g. (0.144 mole) of ethyl γ,γ-diethoxy-α-ethylacetoacetate, 145 ml. of 2 *N* potassium hydroxide solution (0.29 mole) and 125 ml. of methanol was stirred and heated under reflux for 1 hour. After removal of the alcohol through distillation, the alkaline solution was extracted with ether. The extract was dried with sodium sulfate and fractionated to give 16.2 g. (65% yield) of clear liquid boiling at 78–79° (9 mm.), n^{20}_{D} 1.4130, d^{20}_{20} 0.9187, Σ *MR* 47.06, *MR* calcd. 47.21. The reaction of this ketone with dilute ferric chloride solution was very slow; the solution assumed a deep golden brown color in about 30 minutes.

Anal. Calcd. for $C_9H_{18}O_3$: C, 62.02; H, 10.42. Found: C, 61.90; H, 10.16.

Through the usual treatment with potassium cyanide and ammonium carbonate in diluted alcohol, this ketone was converted into **5-diethoxymethyl-5-propylhydantoin**, m.p. 150°.

Anal. Calcd. for $C_{11}H_{20}N_2O_4$: C, 54.05; H, 8.25; N, 11.46. Found: C, 53.98; H, 8.06; N, 11.66.

This ketone reacted with semicarbazide hydrochloride to yield a derivative as a white solid melting with decomposition at 244°. With 2,3-dinitrophenylhydrazine, the ketone yielded a bright orange solid melting with decomposition at 285–286°.

Condensation of Isatin with 1,1-Diethoxy-2-pentanone.—A mixture of 10 g. (0.057 mole) of this ketone and 6.35 g. (0.043 mole) of isatin in 22 ml. of the diluted alcoholic solution of potassium hydroxide and 50 ml. of water was stirred at reflux temperature for 72 hours. On cooling, ether extraction permitted recovery of a small amount of unreacted ketone. Acid was added very slowly; first, inorganic salt precipitated, then an agglutinous red mass (isatin, 3.2 g.). After filtration, the filtrate was made basic with sodium carbonate solution and the volume was reduced by evaporation to 75 ml. The addition of concentrated acid caused separation of spongy, amorphous material. From benzene solution was obtained 3.3 g. (25% yield) of **2-diethoxymethyl-3-ethylcinchoninic acid** as a yellowish solid melting at 145–150°. After recrystallization from a mixture of benzene and Skellysolve A, the acid was obtained as a fibrous, white solid melting at 146.5°.

Anal. Calcd. for $C_{17}H_{21}NO_4$: neut. equiv., 303.2; C, 67.28; H, 6.98; N, 4.62. Found: neut. equiv., 313; C, 67.10; H, 7.10; N, 4.50.

Preparation of 3-Ethyl-2-formylcinchoninic Acid.—Seven hundred fifty milligrams of 2-diethoxymethyl-3-ethylcinchoninic acid was warmed with 60 ml. of 0.25 *N* sulfuric acid until dissolved. After warming on a steam-cone for about 2 hours, a solid product began to appear in the solution; warming was continued for 2 hours. The volume of the solution was reduced before the solution was chilled; about 500 mg. (88% yield) of an acidic solid material was obtained. The latter was recrystallized from hot diluted methyl alcohol to yield a white, crystalline solid which melted with decomposition at 222–223°. This new quinoline derivative gave a positive Schiff test for aldehydic character.[22]

Anal. Calcd. for $C_{13}H_{11}NO_3$: neut. equiv., 229.1; C, 68.09; H, 4.84; N, 6.11. Found: neut. equiv., 232; H, 4.75; N, 6.25.

Attempted Clemmensen Reduction of 3-Ethyl-2-formylcinchoninic Acid.—One-half gram of the formyl acid, 3 g. of amalgamated zinc, 12 ml. of water, 3 ml. of ethyl alcohol and 15 ml. of concentrated hydrochloric acid were heated at reflux temperature for 5.5 hours. The liquid was decanted, diluted with an equal volume of water and sufficient sodium hydroxide solution to precipitate zinc hydroxide; at this point a definite, fragrant odor, suggestive of quinaldine, was noted in the mixture. The latter was subjected to steam distillation and 100 ml. of distillate was collected and extracted with ether. The extract was dried and evaporated to leave a small residuum of light brown oil. The latter yielded a bright yellow, crystalline picrate, melting at 229.0–229.5° dec.

Anal. Calcd. for $C_{18}H_{16}N_4O_7$: N, 14.03. Found: N, 14.07.

These data suggested that the picrate was that of 3-ethyl-2-methylquinoline, obtained earlier in this investigation; a mixture of these two samples melted at 228.5–229.5°.[23]

From the mother liquor, resulting from the steam distillation, was obtained 200 mg. of brown solid; attempts to purify this material were unsuccessful. It charred on burning and, although it had no discrete melting point, it was observed to spread on the melting slide and to undergo extensive decomposition at 260–264°. The latter behavior implied the presence of the expected reduction product, 3-ethyl-2-methyl-cinchoninic acid (which melts with decomposition at 257–258°).

Preparation of 5-Amyl-5-(dimethoxymethyl)-hydantoin.—For the production of the ketone prerequisite for the production of this hydantoin, ethyl γ,γ-diethoxyacetoacetate was alkylated with butyl bromide, in the manner employed for production of the ethyl analog, to form ethyl α-butyl-γ,γ-diethoxyacetoacetate, b.p. 124–127°, n^{20}_{D} 1.4296, d^{20}_{20} 1.001 Σ *MR* 71.81, *MR* calcd. 71.00. The ester developed a russet coloration in dilute ferric chloride solution within two minutes. The ester was hydrolyzed with methanolic potassium hydroxide solution to a liquid distilling at 94° (8–9 mm.) or 222° (atm. press.), n^{20}_{D} 1.427, d^{20}_{20} 0.912, Σ *MR* 56.30, *MR* calcd. 56.90. The 1,1-diethoxy-2-heptanone was treated with potassium cyanide and ammonium carbonate solution in a sealed container at 110° to yield the hydantoin derivative, a white crystalline material melting at 119–120°.

Anal. Calcd. for $C_{13}H_{24}N_2O_4$: N, 10.29. Found: N, 10.56.

An attempt to convert 1,1-diethoxy-2-heptanone into a cinchoninic acid, by condensation with isatin in alkaline solution, failed. However, the lower analog (the dimethoxyheptanone) succeeded.

Preparation of Ethyl α-Butyl-γ,γ-dimethoxyacetoacetate.—Dichloroacetic acid was converted into ethyl dimethoxyacetate, b.p. 57–60° (4–5 mm.), n^{20}_{D} 1.4078, d^{20}_{20} 1.054, Σ *MR* 34.85, *MR* calcd. 34.66.[24]

This ester was condensed with ethyl acetate in the presence of sodium to yield ethyl γ,γ-dimethoxyacetoacetate in 76% yield, b.p. 104.0 ± 0.5° (4 mm.), n^{20}_{D} 1.4286, d^{20}_{20} 1.084, MR_{keto} 44.10, MR_{enol} 45.14, *MR* calcd. 45.15. The ester caused the immediate formation of a blood-red color when shaken with dilute ferric chloride solution.

Anal. Calcd. for $C_8H_{14}O_5$: C, 52.10; H, 7.42. Found: C, (53.5); H, 7.30.

The ester reacted with semicarbazide hydrochloride to form a buff colored solid melting to a char to 227°. The analytical data are indicative of the formation of a disemi-

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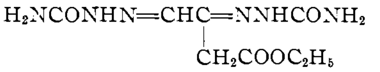
[21] This ester was prepared through the sequence—dichloroacetic acid → ethyl diethoxyacetate → ethyl γ,γ-diethoxyacetoacetate.

[22] To discount the possible erratum of a positive Schiff test due to presence of a tertiary nitrogen atom, as was found to obtain for quinoline and isoquinoline, 3-ethyl-2-methylcinchoninic acid was submitted to this test and found not to react.

[23] Control samples of 2,3-dimethylcinchoninic acid and 3-ethyl-2-methylcinchoninic acid were subjected to the reducing conditions as described above and in both cases small amounts of the corresponding quinolines were obtained. Under the same conditions, however, samples of 2-methylcinchoninic acid and 2-propylcinchoninic acid did not yield quinolines. None of these four cinchoninic acid derivatives was degraded to the corresponding quinolines when treated as described except for the absence of the zinc amalgam.

[24] By treating a sample of ethyl dimethoxyacetate with hot 3 *N* sulfuric acid, the acetal group was hydrolyzed and the resulting formyl compound was characterized as the phenylhydrazone of ethyl glyoxalate, a known compound [A. Steyrer and W. Seng, *Monatsh.*, **17**, 629 (1898)].

carbazone derivative of the dioxo ester, formed as a result of acid cleavage of the acetal group terminal to the ester molecule, namely,



$$H_2NCONHN{=}CHC{=}NNHCONH_2 \quad (CH_2COOC_2H_5 \text{ on } C)$$

Anal. Calcd. for $C_8H_{14}N_6O_4$: C, 37.18; H, 5.46; N, 32.62. Found: C, 37.35; H, 5.42; N, 32.75.

The dimethoxyacetoacetate was alkylated with sodium ethylate and butyl bromide to produce **ethyl α-butyl-γ,γ-dimethoxyacetoacetate**, b.p. 128.5–129.5° (4–5 mm.), n^{20}_{D} 1.4342, d^{20}_{20} 1.019, $\Sigma\ MR_{keto}$ 62.57, $\Sigma\ MR_{enol}$ 63.61, *MR* calcd. 62.90

Anal. Calcd. for $C_{12}H_{22}O_5$: C, 58.48; H, 8.97. Found: C, 58.25; H, 8.81.

Preparation of 1,1-Dimethoxy-2-heptanone.—The dimethoxy ester was hydrolyzed, by heating in diluted methyl alcohol, by means of potassium hydroxide solution to yield (70%) 1,1-dimethoxy-2-heptanone, b.p. 98–100° (4–5 mm.), n^{20}_{D} 1.4218, d^{20}_{20} 0.939, Σ *MR* 47.07, *MR* calcd. 47.10.

This ketone reacted with semicarbazide hydrochloride to form a white crystalline derivative which melted with decomposition at 241.2°. It reacted with 2,4-dinitrophenylhydrazine to yield a fluffy, bright orange powder melting at 185–186°. The ketone reacted with potassium cyanide and ammonium carbonate to yield **5-amyl-5-(dimethoxymethyl)-hydantoin**, melting at 94–95°.

Anal. Calcd. for $C_{11}H_{20}N_2O_4$: N, 11.46. Found: N, 11.38.

Condensation of Isatin with 1,1-Dimethoxy-2-heptanone.—Nine grams (0.051 mole) of the ketone, 5.4 g. (0.036 mole) of isatin, 25 ml. of the 34% potassium hydroxide solution, 45 ml. of water and 25 ml. of ethyl alcohol were stirred and refluxed for 72 hours. In the usual way there was obtained 8 g. (70% yield) of crude product. After recrystallization from benzene–Skellysolve A, **3-butyl-2-dimethoxymethylcinchoninic acid** melted at 155–156°.

Anal. Calcd. for $C_{17}H_{21}NO_2$: neut. equiv., 303.3; N, 4.62. Found: neut. equiv., 296; N, 4.85.

Preparation of 3-Butyl-2-formylcinchoninic Acid.—Three-fourths gram of the dimethoxy acid was dissolved in 75 ml. of 0.4 *N* sulfuric acid and heated on a steam-bath for 5 hours; small quantities of water were added from time to time to keep the volume nearly constant. From the cooled solution was obtained about 0.6 g. (94% yield) of crude product. Recrystallization from hot ethyl alcohol yielded small white crystals which melted with decomposition at 207°. The product reacted with Schiff reagent, and developed a raspberry red coloration in 2 *N* potassium hydroxide solution.

Anal. Calcd. for $C_{15}H_{15}NO_3$: neut. equiv., 257; N, 5.44. Found: neut. equiv., 266.5; N, 5.55.

Attempted Clemmensen Reduction of 3-Butyl-2-formylcinchoninic Acid.—The formyl acid was refluxed in diluted alcoholic solution with concentrated hydrochloric acid and amalgamated zinc. The reaction product behaved like an ethyl ester, therefore, it was redissolved in ethyl alcohol containing sodium hydroxide and refluxed. Upon neutralization, a tan precipitate was recovered. After recrystallization from diluted alcohol, the solid material darkened and melted at 261–264°.

Anal. Calcd. for $C_{15}H_{17}NO_2$: N, 5.95. Found: N, 5.75.

The melting point behavior of a mixture of some of this material with some **3-butyl-2-methylcinchoninic acid**, formed from interaction of isatin and hexyl methyl ketone (m.p. 261–263°), was practically the same as that of either component.

Ultraviolet Absorption Spectra of Substituted Cinchoninic Acid.—The absorption data were obtained for dilute aqueous solutions of the acids through use of a Beckman quartz spectrophotometer, model DU. It was noted that substitution of alkyl groups into the 2-, 3- or 2,3-positions of cinchoninic acid does not significantly change the maximum or minimum points of absorption. On the contrary, the 2-formylcinchoninic acids were observed to exhibit a change, evidently due to a lengthening of the conjugation of unsaturation in such compounds.

X-Ray Diffraction Patterns for Substituted Cinchoninic Acids.—The X-ray diffraction patterns[25] were obtained for the K_α radiation (1.5405 Å.) of copper obtained in a Hayes X-ray diffraction unit operating at 30 kv. and 15 ma. A Spectron recording spectrometer was used for tracing the X-ray intensity in the range of rotation of the mounted sample from 2° to about 50°. The intensity apices of the curves were easily measured in terms of degrees of angle of diffraction. Conversion of these angular values to linear measurements of the distances, *d*, between the unit cell interfaces of the crystalline compound studied was made by the use of a table.[26]

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[25] Appreciation is hereby expressed to Dr. S. H. Simonsen, of the Dept. of Chemistry, The University of Texas, for his aid in securing these X-ray diffraction data.

[26] Tables for Conversion of X-Ray Diffraction Angles to Interplanar Spacing, Applied Mathematics Series 10, National Bureau of Standards, U. S. Department of Commerce, Washington, D. C.

AUSTIN, TEXAS

[CONTRIBUTION FROM THE INSTITUTE FOR INFECTIOUS DISEASES, THE UNIVERSITY OF TOKYO AND NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Studies on Azulenes. I. 2- and 3-Substituted S-Guaiazulene

BY TYUNOSIN UKITA, HIROSHI WATANABE AND MAKOTO MIYAZAKI

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The tertiary alcohol obtained from the reaction of α-kessyl ketone with isopropylmagnesium iodide on dehydrogenation gave 2-isopropyl-S-guaiazulene as the product. In addition S-guaiazulene (1,4-dimethyl-7-isopropylazulene) was obtained. On acetylation S-guaiazulene yielded 3-acetyl-S-guaiazulene and the latter compound was converted to 3-isopropenyl-S-guaiazulene. Catalytic hydrogenation of this substance gave two rearrangement products, 2-isopropenyl- and 2-isopropyl-S-guaiazulene. S-Guaiazulene was also obtained in this case.

Considerable interest has recently been shown in the azulenes. They are more stable than most polyenes and possess properties similar to aromatic compounds.

Because of the interesting chemistry of the azulenes and their known anti-inflammatory action,[1] we undertook a study of a series of these substances.

Recently Herz[2] attempted to prepare 1-isopropyl-4,8-dimethylazulene from 1-isopropyl-4,7-dimethylindan by the ring expansion reaction with diazoacetic ester. However he found that in the dehydrogenation step rearrangement of the isopropyl group occurred to give 2-isopropyl-4,8-dimethylazulene (vetiveazulene). However, 1,4,8-trimethylazulene and 1,3,4,8-tetramethylazulene[3] can be prepared by this procedure without migration of the methyl group. Furthermore Wagner-Jauregg[4]

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[1] C. Pommer, *J. Exptl. Path. Pharmacol.*, **199**, 74 (1942).

[2] W. Herz, THIS JOURNAL, **74**, 1350 (1952); **75**, 73 (1953).

[3] Pl. A. Plattner, A. Fürst and H. Schmidt, *Helv. Chim. Acta*, **28**, 1647 (1945).

[4] T. Wagner-Jauregg, H. Arnold and F. Hüter, *Ber.*, **75**, 1293 (1942).