

Hydrolysis of the 3-Alkyl-3-ethoxycarbonyl-1,2,3,4-tetrahydro-1-hydroxy-2-oxoquinolines. Method D.—The ester to be hydrolyzed was heated under reflux with 5 *N* NaOH (4 ml/g) for a time dependent on the nature of the 3-alkyl group (20 min for ethyl, *n*-propyl, *n*-butyl; 15 min for isopropyl; 10 min for *sec*-butyl and isobutyl). The solution was poured into dilute HCl and ice to yield the corresponding 3-carboxylic acid.

Decarboxylation of the 3-Alkyl-1,2,3,4-tetrahydro-1-hydroxy-2-oxoquinoline-3-carboxylic Acids. Method E.—The carboxylic acid was dissolved in warm diphenyl ether (10 g/g of acid) and the temperature carefully was raised until CO₂ evolution commenced. This temperature was maintained until the decomposition was complete, and the solution was cooled and diluted with ether. The hydroxamic acid was extracted into 1 *N* NaOH and liberated by addition of acid.

Metal Complexes of 2',3'-*O*-Isopropylidene-6-thioinosine^{1a}

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Some metabolic inhibitions brought about by the antineoplastic agent 6-mercaptopurine are attributable to its anabolite, 6-thioinosinic acid.² Among other effects, this nucleotide enhances inhibition of adenylosuccinase by cupric ions,³ possibly by formation of a cupric-6-thioinosinate complex. Isopropylidene-6-thioinosine forms 2:1 complexes with copper and nickel in which the metal is presumably bound to the sulfur and to N-7 of the purine moiety, in analogy to copper and nickel chelates of 8-hydroxyquinoline and a series of aza analogs of 8-hydroxyquinoline related to 6-hydroxypurine.⁴

Experimental Section

Nickel Complex of 9-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)-6-mercaptopurine.—To a solution of 9-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-6-mercaptopurine⁵ (48.6 mg, 0.15 mmole) in water (10 ml) containing 0.15 ml of 1 *N* NaOH was added, at ca. 45°, 0.15 ml of 0.5 *M* NiCl₂. The yellow-green suspension was cooled, extracted with three 25-ml portions of chloroform, and the CHCl₃ solution was washed with water (25 ml), dried (Na₂SO₄), and evaporated to dryness. The dark solid (51 mg) was dissolved in acetone; addition of petroleum ether (bp 40–60°) gave a yellow-green precipitate which was collected by centrifugation and washed with acetone–petroleum ether (1:1).

Anal. Calcd for C₂₆H₃₆N₄NiO₈S₂: C, 44.27; H, 4.29; N, 15.89; Ni, 8.32. Found for material dried at 90° (0.01 mm): C, 44.38; H, 4.55; N, 16.00; Ni, 8.09.

The complex slowly decomposed without melting at 300°. In ethanol, it showed absorption maxima at 228 and 322 mμ, $\epsilon_{228}/\epsilon_{328}$ 0.79, and a minimum at 265 mμ.

Copper complex of 9-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-6-mercaptopurine was prepared from CuSO₄ and the above nucleoside by the procedure used for the nickel complex. The complex was isolated by extraction with chloroform and obtained as a yellow precipitate by addition of petroleum ether to its solution in acetone.

Anal. Calcd for C₂₆H₃₆CuN₄O₈S₂·3CH₃COCH₃: C, 47.53; H, 5.95; Cu, 7.19; N, 12.68. Found for material dried at 60° (0.1 mm): C, 49.34; H, 5.60; Cu, 6.70; N, 13.20.

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The Interaction of Alkyl 2-Naphthyl Ketones with Isatin¹

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Serious pharmacological side effects noted to occur with the administration of 2-phenyleinchoninic acid^{3,4} have led to intensified research in the synthesis of analogs of this compound.^{5,6}

In this investigation, a homologous series of 3-alkyl-2-(2-naphthyl)cinchoninic acids, extended through the hendecyl member, has been prepared under Pfitzinger reaction conditions, which invalidates the assumption of Bua-Hoi, *et al.*,⁷ that compounds of type RCO(CH₂)_{*n*}CH₃ in which R represents a 2-naphthyl group and *n* is an integer greater than 2 would be so sterically hindered that ring closure could not occur.

Experimental Section

C, H, N analyses were performed by Huffman Laboratories, Inc., Wheatridge, Colo. Melting points were determined by the capillary method and are corrected. The molecular weight of each cinchoninic acid was determined by the nonaqueous titration procedures as outlined by Fritz.⁸

General Procedure for 2-Naphthyl Ketone Synthesis.—All ketones in this investigation were prepared in good yield by the interaction of 2-naphthoyl chloride with the appropriate dialkylcadmium reagent.

General Procedure for Preparation of 5-Substituted 5-(2-Naphthyl)hydantoin.—The 300-ml Pyrex liner of a monel-metal bomb was charged with 0.01 mole of a 2-naphthyl ketone dissolved in 100 ml of dimethylformamide (DMF). To this solution was added 1.5 equiv of KCN, dissolved in the least amount of H₂O, and 4 equiv of (NH₄)₂CO₃. The bomb was quickly closed and placed in an oven regulated at 115° for 24 hr. The reaction mixture was then rendered alkaline by the addition of 10% aqueous NaOH and any unreacted ketone was subsequently ether extracted. Acidification of the aqueous layer with concentrated HCl caused precipitation of the hydantoin derivative.

General Procedure for Preparation of 3-Substituted 2-(2-Naphthyl)cinchoninic Acids.—A reaction solvent was prepared from 12 g of 85% KOH, 15 ml of water, and 85 ml of ethyl alcohol. To this solution, 0.05 mole of a 2-naphthyl ketone and 0.07 mole of isatin was added, and the resulting mixture was refluxed for 96 hr with rapid stirring. The ethyl alcohol was then removed by distillation and the residual dark brown solution was diluted with 50 ml of water and ether extracted to remove any unreacted ketone. Adjustment of the pH of the aqueous layer to 8.0 with concentrated HCl produced a gelatinous precipitate which was removed by suction filtration, found to be an inorganic salt, and discarded. Subsequent adjustment of the pH of the filtrate to 5.0 with concentrated HCl resulted in the formation of a thick granular tan precipitate which, after decolorization and recrystallization from ethanol, proved to be the desired cinchoninic acid. Results are summarized in Table I.

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