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 CO_2 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-mercaptopurine[5] (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* $NiCl_2$. The yellow-green suspension was cooled, extracted with three 25-ml portions of chloroform, and the $CHCl_3$ solution was washed with water (25 ml), dried (Na_2SO_4), 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 $C_{26}H_{30}N_8NiO_8S_2$: 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, A_{322}/A_{228} 0.79, and a minimum at 265 mμ.

Copper complex of 9-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-6-mercaptopurine was prepared from $CuSO_4$ 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 $C_{26}H_{34}CuN_8O_8S_2 \cdot 3CH_3COCH_3$: 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 Isatin[1]

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Serious pharmacological side effects noted to occur with the administration of 2-phenylcinchoninic 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 Buu-Hoi, *et al.*,[7] that compounds of type $RCO(CH_2)_nCH_3$ 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 H_2O, and 4 equiv of $(NH_4)_2CO_3$. 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.

(1) Constructed from a portion of the Ph.D. dissertation of R. D. Garrett at the University of Texas.

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TABLE I

3-R-2-(2-NAPHTHYL)CINCHONINIC ACIDS

R	Mp, °C dec	Yield, %	Calcd: Neut equiv	Calcd: C, %	Calcd: H, %	Found: Neut equiv	Found: C, %	Found: H, %
H	245–247[a]	96						
CH_3	289–290[b]	90						
C_2H_5	310–311[c]	62						
n-C_3H_7	262–263	48	341	80.99	5.62	336	80.88	5.24
n-C_4H_9	261–262	51	356	81.09	5.95	353	81.08	5.98
i-C_4H_9	289–290	33	355	81.09	5.95	365	81.28	5.84
n-C_5H_{11}	273–274	56	369	81.27	6.23	367	81.04	6.23
n-C_6H_{13}	255–257	46	384	81.44	6.57	381	81.37	6.47
n-C_7H_{15}	190–191	56	398	81.59	6.85	391	81.55	6.93
n-C_9H_{19}	201–202	28	426	81.83	7.34	422	81.76	7.37
n-$C_{11}H_{23}$	183–184	16	454	82.08	7.77	454	81.86	7.79

[a] P. K. Bose and N. C. Guha [*J. Indian Chem. Soc.*, **13**, 700 (1936)] reported mp 248°. [b] Lit.[7b] mp 285–286°. [c] Lit.[7b] mp 314–315°.

General Procedure for Synthesis of 3-Substituted 2-(2-Naphthyl)quinoline Picrates.—Approximately 1.0 g of a cinchoninic acid was intimately mixed with 0.3 g of copper powder[9] and heated on a sand bath at 1 mm pressure. In most cases, it was necessary for the bath temperature to be 270–300°. Picrate derivatives were obtained by the action of a saturated ethanolic solution of picric acid with each quinoline distillate. Results are shown in Table II.

TABLE II

3-R-2-(2-NAPHTHYL)QUINOLINE PICRATES

R	Mp, °C	N, % Calcd	N, % Found
H	161–162	11.58	11.65
n-C_3H_7	195–196	10.64	10.76
n-C_4H_9	203–204 dec	10.36	10.35
i-C_4H_9	197–198	10.36	10.38
n-C_5H_{11}	190–191	10.11	10.01
n-C_6H_{13}	172–173	9.85	9.76
n-C_7H_{15}	153–154	9.61	9.64
n-C_9H_{19}	127–128	9.17	9.25
n-$C_{11}H_{23}$	107–108	8.77	8.71

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Synthesis of Some 2,5-Diamino-4-*n*-butylamino-6-substituted Pyrimidines[1]

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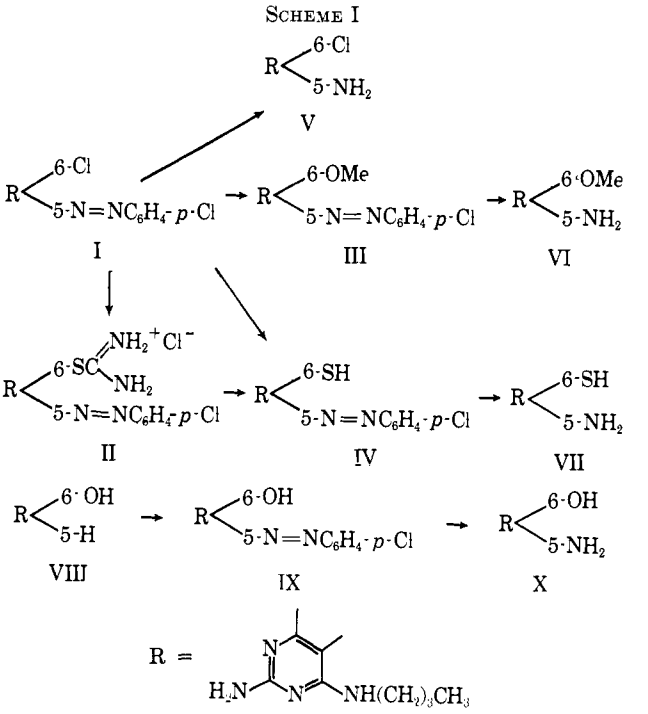
As part of an investigation of potential chemotherapeutic agents, we prepared several new 2,5-diamino-4-*n*-butylaminopyrimidines. Since such compounds are useful intermediates in the synthesis of a variety of heterocyclic systems that are of diverse pharmaceutical interest, we wish to report their preparation and properties.

From the known 2-amino-4-*n*-butylamino-6-chloro-5-(*p*-chlorophenylazo)pyrimidine[3] (I), we prepared the corresponding 6-methoxy (III), and 6-mercapto (IV) analogs (Scheme I); the latter was also obtained from the corresponding isothiouronium chloride (II) which was synthesized by treatment of I with thiourea. 2-Amino-4-*n*-butylamino-5-(*p*-chlorophenylazo)-6-pyrimidinol (IX) was synthesized from 2-amino-4-*n*-butylamino-6-pyrimidinol[4] (VIII) and *p*-chlorophenyldiazonium chloride.

SCHEME I



The 6-methoxy- (VI), 6-mercapto- (VII), and 6-hydroxy-2,5-diamino-4-*n*-butylaminopyrimidines (X) were obtained by reduction of the above 5-*p*-chlorophenylazo derivatives with sodium dithionite. We could not prepare the known 2,5-diamino-4-*n*-butylamino-6-chloropyrimidine[3] (V) by this method; I gave no reaction with sodium dithionite. Moreover, we could not prepare V in satisfactory yields from I by the procedure of Shealy, *et al.*[3] A modification of their procedure gave 46–50% yields of almost pure V.

The instability of 2,5-diamino-4-alkylamino-6-pyrimidinols is well known.[5] Because of their instability, they have been used *in situ*, without isolation. We observed that, on exposure to air and especially on warming, solutions of 2,5-diamino-4-*n*-butylamino-6-pyrimidinol (X) rapidly darkened. However, addition of sodium bisulfite reversed this process and allowed the preparation of analytical samples. The same phenomena were observed to a lesser extent with the 6-methoxy and 6-mercapto analogs.

(1) This work was supported by grant CA-06695 from the National Cancer Institute, Public Health Service, Bethesda, Md.

(2) To whom inquiries should be addressed.

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