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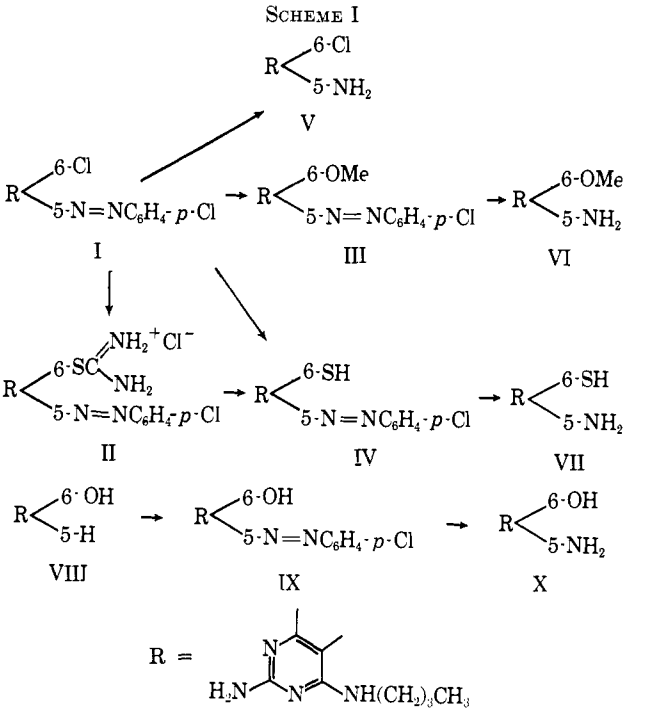
As part of an investigation of potential chemotherapeutic agents, we prepared several new 2,5-diamino-4-*n*-butylaminopyrimidines. Since such compounds are useful intermediates in the synthesis of a variety of heterocyclic systems that are of diverse pharmaceutical interest, we wish to report their preparation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

(3) Y. F. Shealy, R. F. Struck, J. D. Clayton, and I. A. Montgomery, *J. Org. Chem.*, **26**, 4433 (1961).

(4) C. W. Noell and R. K. Robins, *J. Med. Pharm. Chem.*, **5**, 558 (1962).

(5) For example, see H. S. Forrest, R. Hull, H. J. Rodda, and A. R. Todd, *J. Chem. Soc.*, 3 (1951); I. Davoll and D. D. Evans, *ibid.*, 5041 (1960); and W. E. Fidler and H. C. S. Wood, *ibid.*, 4157 (1957).

Experimental Section[6]

2-Amino-4-*n*-butylamino-5-(*p*-chlorophenylazo)pyrimidine-6-isothiouronium Chloride (II).—A mixture of 10.2 g (0.03 mole) of I, 2.44 g (0.03 mole) of thiourea and 150 ml of *t*-butyl alcohol was refluxed with stirring for 1 hr. After cooling to room temperature, 100 ml of acetone was added to the mixture which was then cooled to 5°. The separated, yellow needles were washed with acetone and dried to give 9.75 g (78.2%) of the analytically pure product; mp 203–204°; λ_{max}^{EtOH} 225 mμ (ε 29,500), 261 (17,400), 306 (38,100).

Anal. Calcd for $C_{15}H_{20}Cl_2N_8S$: C, 43.37; H, 4.86; Cl, 17.07; N, 26.98; S, 7.72. Found: C, 43.61; H, 4.90; Cl, 16.95; N, 27.14; S, 7.81.

2-Amino-4-*n*-butylamino-5-(*p*-chlorophenylazo)-6-methoxypyrimidine (III).—A freshly prepared solution of sodium methoxide, from 0.81 g (0.035 mole) of sodium and 60 ml of dry methanol, was added with stirring to a suspension of 10.2 g (0.03 mole) of I in 250 ml of dry methanol, and the reaction mixture was refluxed under a $CaCl_2$ tube for 3 hr. Water (1 ml) was added, and the methanol was distilled until crystallization began; the mixture was cooled gradually to 0°. The separated, yellow needles were washed with cold methanol and dried to give 9.9 g (98%) of the desired product, mp 117–118°. A sample was recrystallized from methanol: mp 118°; λ_{max}^{EtOH} 255 mμ (ε 13,500), 304 (5120), 388 (32,400).

Anal. Calcd for $C_{15}H_{19}ClN_8O$: C, 53.80; H, 5.73; Cl, 10.59; N, 25.10. Found: C, 53.77; H, 5.60; Cl, 10.70; N, 25.00.

2-Amino-4-*n*-butylamino-5-(*p*-chlorophenylazo)-6-pyrimidinethiol (IV). A. From I.—A suspension of 20.3 g (0.06 mole) of I, 14 g (~0.15 mole) of NaHS + aq. (Fisher) in 1700 ml of dry ethanol was refluxed under $CaCl_2$ with vigorous stirring for 12 hr. Another charge of NaHS was then added, and the reaction was continued for an additional 12 hr. The orange solid was separated from the hot reaction mixture by filtration, washed with six 100-ml portions of water followed by three 100-ml portions of ethanol and three 100-ml portions of ether, and dried to give 9.8 g (48.5%) of analytically pure product: mp 212–213°; λ_{max}^{EtOH} 226 mμ (ε 20,100), 261 (8710), 306 (24,900), 427 (18,100).

Anal. Calcd for $C_{14}H_{15}ClN_8S$: C, 49.91; H, 5.10; Cl, 10.52; N, 24.96; S, 9.51. Found: C, 50.05; H, 5.19; Cl, 10.46; N, 25.09; S, 9.53.

B. From II.—A suspension of the thiouronium salt (II) in excess 2 *N* NaOH was vigorously stirred for 15 min at room temperature until a clear solution was obtained. On neutralization with HCl, IV precipitated in quantitative yield.

2-Amino-4-*n*-butylamino-5-(*p*-chlorophenylazo)-6-pyrimidinol (IX).—To a suspension of 10.9 g (0.06 mole) of VIII,[4] 60 g of anhydrous sodium acetate, and 300 ml of 50% aqueous acetic acid at 1–3° was added dropwise over 5 min, a solution of *p*-chlorophenyldiazonium chloride (from 8.3 g (0.065 mole) of *p*-chloroaniline, 4.5 g (0.065 mole) of $NaNO_2$, 15 ml of water, and 120 ml of 2 *N* HCl). The mixture was stirred for 1 hr at 2–3°, and at room temperature for 13 hr. The precipitated, yellow product was washed with water, dried, and recrystallized from a mixture of dimethylformamide and ethanol to give 15.1 g (78%) of yellow needles, mp 273–274°, λ_{max}^{EtOH} 243 mμ (ε 12,500), 251 (12,300), 258 sh (9960), 384 (21,100).

Anal. Calcd for $C_{14}H_{17}ClN_8O$: C, 52.41; H, 5.66; N, 26.12; Cl, 11.04. Found: C, 52.61; H, 5.80; N, 26.18; Cl, 11.11.

4-*n*-Butylamino-2,5-diamino-6-chloropyrimidine (V).[3]—In a 2-l., three-necked, round-bottom flask fitted with a mechanical stirrer, reflux condenser, and two 100-ml, pressure-equalizing, addition funnels, set up in such a manner that a slow stream of nitrogen could blanket the contents of the flask and the funnel, was placed 40 g (0.61 g-atom) of zinc (which had been activated by the method of Baer and Buchnea[7]), 378 ml of water, and 278 ml of ethanol. The rapidly stirred mixture was then brought to reflux under a slow stream of nitrogen, and a warm solution of 15.1 g (0.44 mole) of I in 80 ml of dimethylformamide was added dropwise at such rate that a finely divided suspension was formed. Following the addition of I, 37.8 ml of glacial acetic acid was added in a similar manner over 0.5 hr. After addition of the acid, the mixture was stirred with refluxing under nitrogen for 1 hr, then filtered rapidly while hot. The filtered residue (largely zinc) was washed with three 30-ml portions of ethanol, the washings were added to the filtrate, and the combined solution was cooled under nitrogen to 3–5° in an ice bath. After addition of 6 *N* NaOH to the cold, red solution to a pH of 10, a mixture of 1 g of decolorizing charcoal and 20 g of Celite was added (stirring). After 10 min, the cold suspension was filtered under nitrogen through a bed of Celite, the residue was washed with three 50-ml portions of ethanol, and the filtrate and washings were combined. The red solution was brought to pH 7 by the addition of glacial acetic acid, concentrated *in vacuo* to 400 ml, and cooled to 5°. The dark red, crystalline solid was filtered and immediately stirred with 150 ml of 2 *N* HCl. After the undissolved material was removed by filtration, the filtrate was brought to pH 5 and again filtered. To the light yellow solution was added 6 *N* NaOH with stirring until an off-white solid just started to precipitate; the mixture was cooled slowly to 5°. The light tan crystals were dried to give 4.5 g (48%) of the desired product, mp 125–126° (lit.[3] mp 125–126°).

4-*n*-Butylamino-2,5-diamino-6-pyrimidinethiol (VII).—To a gently boiling suspension of 1.7 g (0.005 mole) of IV in 100 ml of water was added with stirring 5.2 g (0.03 mole) of $Na_2S_2O_4$ in small portions during 5 min. The resulting, light yellow solution was heated with stirring for an additional 20 min. After treatment with decolorizing charcoal, the hot filtrate was cooled in an ice bath; light, lemon yellow needles were separated, washed with water, and dried to give 1.05 g (98%) of analytically pure product, mp 174–175°. The compound gradually darkened and became almost black on storage in a closed sample tube, in the absence of light; $\lambda_{max}^{0.1\ N\ NaOH}$ 225 mμ (ε 12,900), 305 (4570); $\lambda_{max}^{0.1\ N\ HCl}$ 235 mμ (ε 19,500), 311 (24,200).

Anal. Calcd for $C_8H_{15}N_5S$: C, 45.03; H, 7.10; N, 32.84; S, 15.03. Found: C, 44.98; H, 7.18; N, 32.80; S, 15.11.

4-*n*-Butylamino-2,5-diamino-6-methoxypyrimidine (VI) was prepared from III by a method similar to that described for the 6-mercapto analog (VII) except that the reaction was carried out in 50% aqueous ethanol. After concentration *in vacuo* and cooling, the analytically pure product separated in 63% yield: mp 112–113.5°; λ_{max}^{EtOH} 286 mμ (ε 8250), 302 (6780).

Anal. Calcd for $C_9H_{17}N_5O$: C, 51.11; H, 8.14; N, 33.18. Found: C, 50.95; H, 7.99; N, 33.38.

4-*n*-Butylamino-2,5-diamino-6-pyrimidinol (X) was prepared from IX by essentially the same procedure as the 6-methoxy analog (VI) except that 70% aqueous ethanol was employed as the solvent at a reaction temperature of 70–75°; yield 83.5%, mp 206–208° dec. While the solid appeared to be indefinitely stable, solutions of the compound darkened in the presence of air, especially on warming. This color change could be reversed by adding a small amount of $Na_2S_2O_4$ or $NaHSO_3$ to the dark solution (stirring). To prepare an analytical sample, the compound was stirred at room temperature with a small volume of ethanol containing some $NaHSO_3$. The saturated, alcoholic solution was then rapidly filtered at room temperature under nitrogen. Upon cooling to −15°, a yellow solid separated which was dried at room temperature *in vacuo*; mp 208–210° dec; λ_{max}^{EtOH} 294 mμ (ε 7190), 367 sh (1880).

Anal. Calcd for $C_8H_{15}N_5O$: C, 48.70; H, 7.68; N, 35.51. Found: C, 48.56; H, 7.49; N, 35.70.

(6) Melting points are uncorrected. All ultraviolet spectra were determined with a Cary 15 spectrophotometer. Elemental analyses are by Galbraith Laboratories, Inc., Knoxville 21, Tenn.

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N-(2-Chloroethyl)-DL-aspartic Acid and Some Related Amino Acids

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Mutagenic effects on Drosophila are shown by many monofunctional alkylating agents.[1] Falmy and Fahmy[2] pointed out that mutagenicity with the mustards is influenced not only by

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(2) (a) O. G. Fahmy and M. J. Fahmy, *J. Genet.*, **54**, 146 (1956); (b) *Genet. Res.*, **1**, 173 (1960); (c) *Heredity*, **15**, 115 (1960); (d) *Genetics*, **46**, 1141 (1961).