of fraction 3 gave the following bands (in microns)[22]: 3.43vs, 3.51vs, 2.90 vw, 5.72vs, 5.83s, 6.81s, 6.94 ms, 7.25m, 7.70m, 7.82m, 8.05m, 8.17m, 8.33m, 8.42m, 8.52ms, 8.92m, 9.07w, 9.65w, 10.62ms, 11.27w, 13.14w, 13.70m, 13.87ms and 14.52w. The spectrum is in agreement with a non-conjugated long chain ketoester.

The ultraviolet absorption spectrum of fraction 3 in absolute methanol (0.8 mg. of lipid per ml. of methanol) showed a single peak at 229 mμ which was nearly abolished after reduction with hydrogen. The sulfuric acid chromogen of fraction 3 was prepared as described by Zaffaroni[23] at a concentration of 90 μg. per 3 ml. of sulfuric acid. A single peak was found at 306 mμ. The ultraviolet spectra were determined with a Beckman DU spectrophotometer.

Alkali Isomerization of the Fatty Acids of Fraction 3.—The fatty acids obtained by the alkaline hydrolysis of fraction 3 were isomerized with glycerol–KOH according to the procedure of Collins and Sedgwick.[24] The ultraviolet spectrum which was run at a concentration of 73 μg. per ml. of solution, showed a major peak at 232 mμ and a small peak at 268 mμ but no absorption band between 290 to 320 mμ. Pure samples of linoleic and linolenic acid were run simultaneously. Linoleic acid gave the characteristic diene peak at 232 mμ whereas linolenic acid showed the typical triene peak at 268 mμ and also a small peak at 232 mμ. The spectral results indicate that the fatty acids from fraction 3 are predominantly dienoic acids but that smaller amounts of trienoic acids are also present. However, little, if any, tetraenoic acid occurs in this fraction. The dienoic and trienoic acids are not exclusively linoleic and linolenic acids as shown by paper chromatographic studies but rather are either unsaturated acids having 20 or more carbon atoms or are unsaturated keto acids.

Paper Chromatographic Analysis.—Paper chromatography of fraction 3 and the petroleum ether extractable material obtained after the alkaline hydrolysis of fraction 3 was carried out in three solvent systems. The first system (solvent I) was methanol–water 9:1 and utilized Whatman no. 1 filter paper impregnated with 10% mineral oil as described by Ashley and Westphal.[25] The second system (solvent II) was acetic acid–water 9:1[26] and also utilized filter paper impregnated with 10% mineral oil. The third system which was developed in this Laboratory consisted of isoöctane–acetone–acetic acid 95:4:1 and required silicic acid impregnated paper which was prepared as described previously.[27]

Fraction 3 gave one major spot (R_f 0.61) and a trace spot (R_f 0.42) in solvent III. The major spot moved in a manner similar to methyl linoleate (R_f 0.58) whereas the trace spot moved the same as stearic acid (R_f 0.42). In this system monopalmitin and tripalmitin had R_f values of 0.00 and 0.72, respectively, whereas oleyl–stearyl diglyceride had an R_f value of 0.59.

The petroleum ether extractable material from the hydrolysis of fraction 3 gave 4 spots in solvent I (R_f values of 0.40, 0.54, 0.67 and 0.84). All spots except the fastest moving one gave a positive test with brom thymol blue. Hence the three slower moving components are fatty acids and the fastest moving component is believed to be a long chain alcohol. Furthermore, all spots except the slowest moving one gave a positive test with $KMnO_4$. Moreover, after reduction with hydrogen, the spots having R_f values of 0.54 and 0.67 were transformed into a saturated fatty acid which had an R_f value of 0.33. The R_f values of stearic, linoleic and linolenic acids in this system were 0.39, 0.59 and 0.67, respectively.

In solvent II, the petroleum ether extractable material gave 5 spots having R_f values of 0.10, 0.19, 0.30, 0.48 and 0.79. All components except the fastest moving one gave a positive test with brom thymol blue and all components except the two slowest moving ones gave a positive test with $KMnO_4$. After reduction with hydrogen the components having R_f values of 0.30 and 0.48 were transformed into a saturated fatty acid having an R_f value of 0.10. The R_f values of stearic, linoleic and linolenic acids in this system were 0.17, 0.39 and 0.48, respectively.

The chromatographic analysis indicates that two fatty acids of fraction 3 are stearic and linolenic acid. Another component moves similarly but not identically with linoleic acid. The finding that the unsaturated acids are converted, after reduction, to a saturated acid having an R_f value less than that of stearic acid demonstrates that the major part of the unsaturated acids contain 20 or more carbon atoms and hence cannot be linoleic or linolenic acids. The fastest moving component which fails to give a positive test with brom thymol blue is believed to be an unsaturated high molecular weight alcohol.

(22) The abbreviations have the following designation: s, strong; vs, very strong; m, moderate; w, weak; ms, moderately strong, vw, very weak.

(23) A. Zaffaroni, THIS JOURNAL, **72**, 3828 (1950).

(24) F. I. Collins and E. Sedgwick, *J. Amer. Oil Chem. Soc.*, **33**, 149 (1956).

(25) B. D. Ashley and U. Westphal, *Arch. Biochem. Biophys.*, **56**, 1 (1955).

(26) H. P. Kaufmann and W. H. Nitsch, *Fette und Seifen*, **56**, 154 (1954).

(27) G. V. Marinetti and E. Stotz, *Biochim. Biophys. Acta*, **21**, 168 (1956).

ROCHESTER, N. Y.

[CONTRIBUTION FROM THE KETTERING–MEYER LABORATORY,[1] SOUTHERN RESEARCH INSTITUTE]

Synthesis of Potential Anticancer Agents. XI. $N^{2,6}$-Alkyl Derivatives of 2,6-Diaminopurine[2]

BY JOHN A. MONTGOMERY AND LEE B. HOLUM

RECEIVED AUGUST 26, 1957

Several $N^{2,6}$-alkyl derivatives of 2,6-diaminopurine have been prepared by the stepwise reaction of aliphatic amines with 2,6-dichloropurine. The 6-alkylamino-2-chloropurines failed to react with aqueous ammonia, but the desired 2-amino-6-alkylaminopurines were successfully prepared from 2-amino-6-methylthiopurine. During the course of this work an improved procedure for the preparation of 2,6-dichloropurine was developed.

As a part of our general program to exhaustively investigate purines in search of more effective anticancer agents, we have prepared a number of alkyl derivatives of 2,6-diaminopurine. 2,6-Diaminopurine itself has been shown to possess some anticancer activity[3] and is known to be incorporated into nucleic acids as guanylic acid.[4] Although a number of 6-alkylaminopurines have been prepared, the synthesis of only a few $N^{2,6}$-alkyl-2,6-

(1) Affiliated with the Sloan-Kettering Institute. This work was supported by funds from the C. F. Kettering Foundation.

(2) Part X, J. A. Montgomery and Kathleen Hewson, THIS JOURNAL, **79**, 4559 (1957).

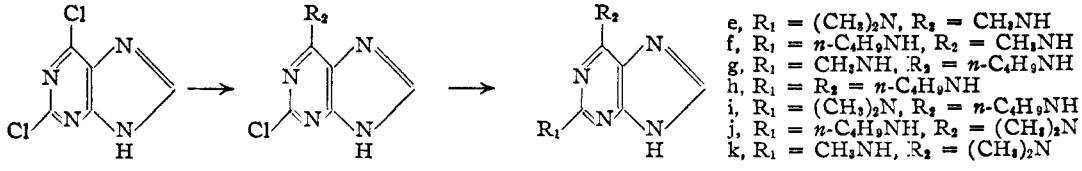
(3) J. H. Burchenal, A. Bendich, G. B. Brown, G. B. Elion and G. H. Hitchings, *Cancer*, **2**, 119 (1949).

(4) L. L. Bennett, Jr., H. E. Skipper, C. C. Stock and C. P. Rhoads, *Cancer Research*, **15**, 485 (1955).

diaminopurines can be found in the literature.[5]

Since a relatively large amount of 2,6-dichloropurine (I) was necessary for the preparation of all the desired compounds, an effort was made to improve the original synthesis[6] devised for this compound. This synthesis consisted of cyclization of 4,5-diamino-2,6-dichloropyrimidine to a mixture of 2,6-dichloropurine and N-acetyl-2,6-dichloropurine by means of a 1:1 mixture of acetic anhydride and ethyl orthoformate followed by hydrolysis of the N-acetylpurine in dilute sodium hydroxide solution. First, it was found that formation of the N-acetylpurine, which necessitated hydrolysis, could be avoided by the use of less acetic anhydride, but a higher yield of the purine was still desirable.

Post and Erickson's[7] investigation of the acetic anhydride catalyzed reactions of ethyl orthoformate with active methylene compounds such as



I

IIa, R_2 = NH_2
b, R_2 = CH_3NH
c, R_2 = $(CH_3)_2N$
d, R_2 = n-C_4H_9NH

IIIa, R_1 = CH_3NH, R_2 = NH_2
b, R_1 = $(CH_3)_2N$, R_2 = NH_2
c, R_1 = n-C_4H_9NH, R_2 = NH_2
d, R_1 = R_2 = CH_3NH
e, R_1 = $(CH_3)_2N$, R_2 = CH_3NH
f, R_1 = n-C_4H_9NH, R_2 = CH_3NH
g, R_1 = CH_3NH, R_2 = n-C_4H_9NH
h, R_1 = R_2 = n-C_4H_9NH
i, R_1 = $(CH_3)_2N$, R_2 = n-C_4H_9NH
j, R_1 = n-C_4H_9NH, R_2 = $(CH_3)_2N$
k, R_1 = CH_3NH, R_2 = $(CH_3)_2N$

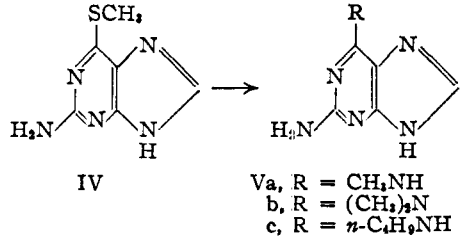
acetoacetic ester showed that this reaction probably proceeds *via* the intermediate diethoxymethyl acetate, which they prepared and isolated from the reaction of acetic anhydride and ethyl orthoformate. Since it seemed reasonable that this same intermediate played a part in the ring closure of the chloro-4,5-diaminopyrimidines to purines, some of this material was prepared and allowed to react with 4,5-diamino-2,6-dichloropyrimidine at 120°. This procedure gave 2,6-dichloropurine in 85–90% yield, consistently, using excess diethoxymethyl acetate as solvent or using three moles of diethoxymethyl acetate and ethyl orthoformate as solvent. It is much superior to the original synthesis. Further investigation of the use of diethoxymethyl acetate in cyclizations is now underway.

Reaction of 2,6-dichloropurine with refluxing aqueous solutions of monomethylamine, dimethylamine and n-butylamine resulted in replacement of one of the chlorine atoms giving good yields of 2-chloro-6-methylaminopurine (IIb), 2-chloro-6-dimethylaminopurine (IIc) and 6-n-butylamino-2-chloropurine (IId). 2-Chloroadenine (IIa) has been prepared previously.[8] This assignment of structure of these compounds was made on the basis of the established fact that the 6-chloride atom of 2,6-dichloropurine is much more reactive than the 2-chlorine atom,[8] and by a comparison of the ultraviolet spectra of these compounds (IIb,c,d) with the corresponding 2- and 6-alkylaminopurines (see below).

(5) R. K. Robins and B. E. Christensen, THIS JOURNAL, **74**, 3624 (1952).
(6) J. A. Montgomery, *ibid.*, **78**, 1928 (1956).
(7) H. W. Post and E. R. Erickson, *J. Org. Chem.*, **2**, 260 (1937).
(8) J. A. Montgomery and L. B. Holum, THIS JOURNAL, **79**, 2185 (1957).

The 2-chloro-6-alkylaminopurines were then allowed to react with aqueous solutions of the above amines in a stainless steel bomb at 130° for 16 hours to prepare the N^{2,6}-alkyl-substituted diaminopurines (IIIa-k). Replacement of the 2-chlorine atom of the 2-chloro-6-alkylaminopurines with aqueous ammonia under the same conditions could not be accomplished. The desired 2-amino-6-alkylaminopurines (Va,b,c) were successfully prepared from 2-amino-6-methylthiopurine using these conditions.

The replacement of the 2-chlorine atom and the 6-methylthio group is more difficult than the replacement of the 6-chlorine atom, as indicated by the conditions necessarily employed, and the yields were lower than those obtained in the replacement of the 6-chlorine atom. Replacement could be accomplished with alcohol solutions of the amines, but this procedure resulted in highly



IV

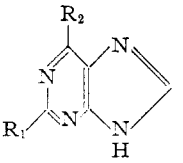
Va, R = CH_3NH
b, R = $(CH_3)_2N$
c, R = n-C_4H_9NH

colored products which could not be satisfactorily purified. Dilute aqueous solutions of 2–3 equivalents of amine to 1 equivalent of purine gave more satisfactory results because the products, which are easily oxidized in basic solution, precipitated from solution either during reaction or upon removal of the excess amine *in vacuo*. The precipitated purines could then be filtered off, washed free of amine with water, and dried. When the alcohol solutions were employed, precipitation did not occur, and it was necessary to evaporate the solutions to dryness *in vacuo* to obtain the solid purines. During the concentration process the solutions turned dark, and the highly colored products mentioned above resulted.

The yields, melting points, recrystallization solvents and elemental analyses of all the purines prepared are recorded in Table I. Examples of typical procedures are given in the Experimental section.

Spectra.—The ultraviolet spectra of the three 6-alkylamino-2-chloropurines are similar to those of the corresponding 6-alkylaminopurines in that they have one strong maximum between 265 and 285 mμ. In contrast, the spectra (at 3 *p*H's) of one of these compounds, 2-chloro-6-dimethylaminopurine, are quite different from those of 2-dimethylamino-

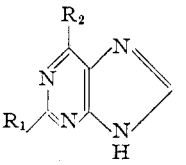
TABLE I



R_1	R_2	Yield, %	M.p., °C.	Recrystn. solvent[a]	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Cl	CH_3NH	77.5	>220[b]	A	39.25	39.22	3.30	3.41	38.15	37.70
Cl	n-C_4H_9NH	82	>300	B	47.90	48.13	5.36	5.45	31.04	30.85
Cl	$(CH_3)_2N$	84	240–280	C + D	42.55	42.30	4.08	4.18	35.45	35.25
NH_2	CH_3NH[c]	39	>300	E	37.77	37.88	5.75	5.21	44.00	43.66
NH_2	n-C_4H_9NH	35	165–166	F	52.41	52.43	6.84	6.56	40.75	40.61
NH_2	$(CH_3)_2N$	71	>300	..[d]	47.18	47.04	5.66	6.28	47.17	46.76
CH_3NH	NH_2	76	>300	..[e]	43.89	44.08	4.91	5.22	51.20	50.77
n-C_4H_9NH	NH_2	66	218–218.5	C + B	52.41	52.24	6.84	6.88	40.75	40.28
$(CH_3)_2N$	NH_2	44	>300	E	47.18	47.23	5.66	5.39	47.17	47.23
CH_3NH	CH_3NH	58	>300	..[e]	47.18	47.36	5.66	5.28	47.17	46.96
n-C_4H_9NH	CH_3NH	33	254–254.5	B	54.52	54.53	7.32	7.33	38.16	37.89
$(CH_3)_2N$	CH_3NH	77	>300	B	49.98	50.42	6.29	6.23	43.72	43.34
CH_3NH	n-C_4H_9NH	65	152[f]	E	54.52	54.50	7.32	7.15	38.16	37.85
n-C_4H_9NH	n-C_4H_9NH[g]	52	274–275	B	52.24	52.04	7.75	7.33	28.13	28.18
$(CH_3)_2N$	n-C_4H_9NH	64	172[f]	B + G	56.38	56.48	7.74	7.65	35.87	35.82
CH_3NH	$(CH_3)_2N$	74	234[f]	E	49.98	49.91	6.29	5.90	43.72	43.13
n-C_4H_9NH	$(CH_3)_2N$	57	177–177.5	B	56.38	56.22	7.74	7.40	35.87	36.17

[a] A, glacial acetic acid; B, ethanol; C, benzene; D, methyl Cellosolve; E, water; F, chloroform; G, carbon tetrachloride. [b] Sublimes. [c] Isolated as a hydrate, elemental percentages calcd. for $C_6H_8N_6 \cdot 1.5H_2O$. [d] Purified by vacuum sublimation. [e] Not recrystallized. [f] Taken on a Kofler Heizbank. [g] Prepared from 2,6-dichloropurine and isolated as the hydrochloride, elemental percentages calcd. for $C_{13}H_{22}N_6 \cdot HCl$.

TABLE II



R_1	R_2	0.1 N HCl λmax, mμ	0.1 N HCl ε × 10⁻³	pH 7 λmax, mμ	pH 7 ε × 10⁻³	0.1 N NaOH λmax, mμ	0.1 N NaOH ε × 10⁻³
H	$(CH_3)_2N$	277	15.6[a]	275[b,c]	17.8	221[b]	16.2
						281	17.8
Cl	$(CH_3)_2N$	285	13.6	277	18.3	284	17.1
$(CH_3)_2N$	H	228	33.1	223	25.7	232	24.6
		248[d]	9.33	248	10.5		
		340	2.80	332	5.12	327	4.67
H	CH_3NH	267	14.9[a]	266[b,e]	16.2	273[b,f]	15.8
Cl	CH_3NH	273	14.4	271	15.0	226	5.34
						272	15.3
H	n-C_4H_9NH	269	16.2	267	16.9	273	17.1
Cl	n-C_4H_9NH	276	15.7	272	17.3	278	16.5

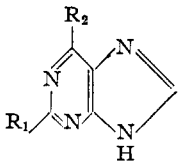
[a] G. B. Elion, E. Burgi and G. H. Hitchings, THIS JOURNAL, **74**, 413 (1952). [b] S. F. Mason, *J. Chem. Soc.*, 2071 (1954). [c] *p*H 6.98. [d] Point of inflection. [e] *p*H 7.12. [f] *p*H 12.

purine, the only 2-alkylaminopurine whose spectra were available for comparison. The spectra of the latter compound have an intense maximum at 225–230 mμ, a medium intensity point of inflection or shoulder about 250 mμ and a weak maximum at 325–340 mμ. These comparisons can be seen in Table II. Mason has discussed the differences in the ultraviolet spectra of 2- and 6-substituted purines.[9]

Table III presents the ultraviolet spectra of the $N^{2,6}$-alkyl derivatives of 2,6-diaminopurine. As might be expected, the ultraviolet spectra of all these compounds are similar to those of 2,6-diaminopurine, but certain differences can be correlated with the position of the alkyl group or groups. Alkylation of the 6-amino group results in variable shifts of the position of the maxima, but in all cases increases the intensity of both maxima. Alkylation of the 2-amino group causes a shift of 5–11 mμ toward the longer wave length in the position of both maxima, increases the intensity of the lower wave length maximum, and decreases the intensity of the higher wave length maximum. The effects caused by alkylation of the 6-amino group predominate over those caused by alkylation of the 2-amino group as shown by the fact that the spectra of the 2-alkylamino-6-alkylaminopurines resemble those of the 2-amino-6-alkylaminopurines as described above.

(9) See Table II, Footnote *b*.

TABLE III



R_1	R_2	0.1 N HCl λmax, mμ	0.1 N HCl ε × 10⁻³	pH 7 λmax, mμ	pH 7 ε × 10⁻³	0.1 N NaOH λmax, mμ	0.1 N NaOH ε × 10⁻³
NH_2	NH_2	242	9.72[a]	247	7.57	243[b]	4.95
		282	9.71	280	9.05	284	9.28
NH_2	CH_3NH	246	12.5	259.5[b]	17.4		
		277	13.7	274	19.4	282	13.7
NH_2	n-C_4H_9NH	247	12.7	254	8.18		
		279.5	13.8	280.5	12.7	285.5	12.8
NH_2	$(CH_3)_2N$	231	12.1	227.5	19.9		
		255.5	15.0	255	10.5		
		281.5	15.3	283	14.4	289	13.8
CH_3NH	NH_2	240[b]	10.9	248	8.55		
		288	7.80	286	6.81	289.5	7.19
n-C_4H_9NH	NH_2	240[b]	13.1	248	10.6		
		288	6.47	286	7.46	289	7.71
$(CH_3)_2N$	NH_2	228	20.0	226	23.8		
		244[b]	14.5	249	11.8		
		292	8.6	293	7.40	295	7.46
CH_3NH	CH_3NH	232	15.5	227	15.1		
		247	13.8	249[b]	9.75		
		286	10.8	285	9.62	290	9.93
n-C_4H_9NH	CH_3NH	233	16.9	228.5	23.2		
		247	15.1	249[b]	10.5		
		285	11.1	285.5	9.56	290	9.84
$(CH_3)_2N$	CH_3NH	236	19.3	234.5	22.6	228	28.6
		248[b]	17.8				
		286	11.2	290	9.24	295	8.60
CH_3NH	n-C_4H_9NH	233.5	15.3	229	22.4		
		249	15.2	248[b]	11.0		
		284	11.6	284	10.5	289	10.7
n-C_4H_9NH	n-C_4H_9NH	236	17.2	231	23.4		
		253	20.0	250[b]	13.9		
		282	14.9	284	12.2	288	12.4
$(CH_3)_2N$	n-C_4H_9NH	238	19.4	237	23.6	238	22.6
		254	21.0				
		283	13.9	292	10.0	291	10.1
CH_3NH	$(CH_3)_2N$	256.5	16.5	251[b]	14.0	251[b]	13.0
		285	13.1	287.5	12.1	288	11.5
n-C_4H_9NH	$(CH_3)_2N$	237	13.6	237	12.3		
		259	16.8				
		285	12.7	290	11.0	295.5	11.2

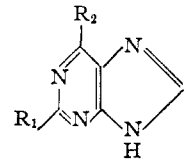
[a] These values are in agreement with those of L. F. Cavalieri, A. Bendich, J. F. Tinker and G. B. Brown, THIS JOURNAL, **70**, 3875 (1948). [b] Point of inflection.

The important absorption bands in the hydrogen stretching and double bond regions of the infrared spectra of these purines are listed in Table IV. With the exception of the spectrum of 2-chloro-6-dimethylaminopurine (which has no amino N–H bonds), the spectra exhibit N–H stretching absorption between 3450 and 3100 cm.$^{-1}$. All the spectra have absorption maxima between 3180 and 2920 cm.$^{-1}$ due to CH vibrations, and they all exhibit the typical, weak absorption between 2800–2400 cm.$^{-1}$ from the acidic hydrogen on the 9-nitrogen of the purines. The spectra of the purines having a primary amino group in the 6-position show strong absorption between 1670–1650 cm.$^{-1}$ probably due to N–H deformation. A primary amino group in the 2-position causes absorption due to N–H deformation at a more normal frequency, 1650–1620 cm.$^{-1}$. Absorption maxima caused by ring vibrations (C=C, C=N) occur in all the spectra between 1630 and 1495 cm.$^{-1}$. In general, the introduction of an amino or alkylamino group into the pyrimidine ring of purine changes the rather sharp bands caused by the truly aromatic double bond vibrations to a broad band with shoulders, which peaks around 1600 cm.$^{-1}$. This change is undoubtedly a reflection of a decrease in the aromatic character of the pyrimidine ring due to the contribution of resonance structures containing the imino group.[10]

Acknowledgment.—The authors are indebted to Mr. J. P. Holmquist for the microanalytical results reported, to Mr. L. D. Norton and Mr. W. A.

(10) C. H. Willits, J. C. Declus, K. L. Dille and B. E. Christensen, THIS JOURNAL, **77**, 2569 (1955).

TABLE IV



R_1	R_2	Important absorption bands, cm.$^{-1}$									
		νNH		νCH		νAcidic NH	δNH		νC=C, C=N		
Cl	NH_2	3400[a]	3280	3110		2800–2400	1670	1634		1590	
Cl	CH_3NH		3200[a]	2980		2800–2400			1620	1590[a]	1550
Cl	n-C_4H_9NH		3170[a]	2920		2800–2400		1630[a]	1620	1590[a]	1555
Cl	$(CH_3)_2N$			3070	2920	2800–2500				1580	1540[a]
NH_2	NH_2	3420	3130	3100		2800–2400	1650[a]		1620[a]	1605	1580[a]
CH_3NH	NH_2	3420	3130[a]	3080		2800–2500	1660	1630		1590	1550
n-C_4H_9NH	NH_2	3420	3260	3070	2920	2800–2500	1635[a]		1620	1580	1530
$(CH_3)_2N$	NH_2	3445	3270	3100		2800–2400	1650[a]		1625	1580	1530
NH_2	CH_3NH	3420	3235	3110		2800–2400	1650[a]		1625[a]	1600	1540[a]
NH_2	n-C_4H_9NH	3420	3280	3180	2920	2800–2500	1635[a]			1600	1560[a]
NH_2	$(CH_3)_2N$	3400		3170	3080	2800–2500	1630[a]			1580	1560[a]
CH_3NH	CH_3NH	3365	3250	3050	2955	2800–2500		1630[a]		1605	1500
n-C_4H_9NH	CH_3NH	3440	3265	3060	2910	2800–2500			1620[a]	1605	1495[a]
$(CH_3)_2N$	CH_3NH		3270	3050	2880	2800–2500		1620[a]	1600	1540	1510
CH_3NH	n-C_4H_9NH	3425	3230	3030	2890	2800–2500			1620[a]	1600	1495
n-C_4H_9NH	n-C_4H_9NH		3200	3020	2935	2800–2500		1630		1580	1520
$(CH_3)_2N$	n-C_4H_9NH		3200[a]	3050	2920	2800–2500	1650[a]		1615	1580	1495
CH_3NH	$(CH_3)_2N$	3420		3090	2910	2800–2600			1610	1580	1510
n-C_4H_9NH	$(CH_3)_2N$	3390		3060	2920	2800–2500			1610	1580	1500

[a] Shoulder

Rose for the spectral determinations, and to Dr. W. C. Coburn, Jr., for his help in the interpretation of the infrared spectra.

Experimental

Except where indicated, melting points were determined on a Fisher–Johns melting point apparatus. The ultraviolet spectra were determined with a Beckman model DK-2 spectrophotometer. The infrared spectra were run in pressed potassium bromide pellets with a Perkin-Elmer model 21 spectrophotometer.

2,6-Dichloropurine[6] **(I).** (A).—A solution of 4,5-diamino-2,6-dichloropyrimidine (500 mg., 2.8 mmoles) in a mixture of ethyl orthoformate (7 g., 47 mmoles) and acetic anhydride (4.8 g., 47 mmoles) was refluxed for one hour, cooled, and the volatiles removed *in vacuo*. The light tan residue was recrystallized from methanol; yield 321 mg. (64%), m.p. 179–180°.

(B).—4,5-Diamino-2,6-dichloropyrimidine (500 mg., 2.8 mmoles) in 10 ml. of diethoxymethyl acetate was heated with stirring for two hours at 100–120°. The solid dissolved shortly after the heating began. The volatiles were removed *in vacuo*, and the residue was recrystallized from methanol; yield 468 mg. (89%), m.p. 179–180°.

2-Chloro-6-dimethylaminopurine (IIc).—A solution of 2,6-dichloropurine (1.00 g., 5.3 mmoles) in 36 ml. of 25% aqueous dimethylamine was refluxed for one hour. After chilling the solution, the solid which had crystallized was removed by filtration, washed with several portions of cold water, and dried thoroughly *in vacuo* over P_2O_5; yield 0.68 g.

Concentration of the filtrate from above gave 0.30 g. of impure product. This material on recrystallization from benzene–methyl Cellosolve gave 0.20 g. of pure material. The total yield of pure 2-chloro-6-dimethylaminopurine was 0.88 g.

6-Amino-2-methylaminopurine (IIIa).—A solution of 2-chloroadenine (3.50 g., 20.6 mmoles) in 140 ml. of 20% aqueous methylamine was heated at 130° for 16 hours in two 100-ml. stainless steel bombs.[11] Upon removal of the excess methylamine *in vacuo*, a white, crystalline solid precipitated. After acidification of the mixture with glacial acetic acid, the white solid was collected by filtration, washed thoroughly with cold water, and dried for several hours over P_2O_5 *in vacuo* at 110°. The yield of pure material was 1.78 g. An additional 0.75 g. of pure material was obtained from the filtrate making the total yield 2.53 g.

2-Amino-6-*n*-butylaminopurine (Vc).—A solution of 2-amino-6-methylthiopurine[8] (4.00 g., 22.1 mmoles) in 100 ml. of 40% (by volume) aqueous *n*-butylamine was heated at 130° for 16 hours in two 100-ml. stainless steel bombs. The resulting solution was concentrated *in vacuo* to remove most of the excess *n*-butylamine and then acidified to *p*H 6 with glacial acetic acid. The light tan solid which crystallized from solution was removed by filtration, washed with water, and air-dried; yield 2.09 g., m.p. 154–155°. An additional 0.70 g. of product, m.p. 164–165°, crystallized from the chilled filtrate.

The first crop was recrystallized from 350 ml. of chloroform; yield 0.89 g., m.p. 165–166°. The total yield of pure material was 1.59 g.

BIRMINGHAM 5, ALABAMA

(11) Parr Instrument Co.