and atmospheric pressure. When one mole of hydrogen had been absorbed, the reaction was stopped and the catalyst and solvent were removed. This afforded 320 mg. of a colorless oil which was taken up in a benzene–petr. ether mixture and chromatographed over alumina (*Woelm*, activity II). The principal eluate fraction yielded 245 mg. of a colorless oil which was dissolved in 5 ml. of acetone and treated with a solution of 500 mg. of dibenzoyl-D-(−)-tartaric acid in 5 ml. of ethyl acetate. When the resulting solution was allowed to stand overnight, there separated 490 mg. of crystals, m.p. 150–151°, unchanged by recrystallization from an acetone–methanol mixture, $[\alpha]^{20}D$ −45° (*c* 1.02, chloroform). A comparison of the dibenzoyl D-(−)-tartrate of XII, prepared in this way, showed it to have an infrared spectrum superimposable with that of (−)-14,15,-16,17-tetrahydro-16-oxaerythrinane (XII) obtained by synthesis. Also, a mixture of the two samples showed no depression of melting point.

For further proof of identity, 470 mg. of the dibenzoyl D-(−)-tartrate of anhydro-α-hexahydrodesmethoxy-β-erythroidinol was dissolved in chloroform and passed over alumina. The free base, obtained by concentration of the chloroform eluate, was treated with ethanolic picric acid to give 300 mg. of yellow crystals, m.p. 202°. These, after a further recrystallization from an acetone–ethanol mixture, melted at 204°. Comparison of this picrate of XII from the natural series with the picrate of (−)-14,15,16,17-tetrahydro-16-oxaerythrinane obtained by synthesis showed them to have identical infrared spectra and mixtures showed no depression of melting point.

A solution of 120 mg. of the pure picrate of anhydro-α-hexahydro-β-erythroidinol in chloroform was passed over alumina and the chloroform eluate was carefully concentrated. This gave 60 mg. of a colorless oil; $\alpha^{25}D$ −110° (*c* 0.6 in $CHCl_3$), b.p. (short path still) 110–120° at 10^{-4} mm.

Anal. Calcd. for $C_{15}H_{23}NO$: C, 77.20; H, 9.94; N, 6.00. Found: C, 76.85; H, 10.04; N, 5.94.

N-(2*H*-5,6-Dihydropyranyl-3-acetyl)-hexahydroindole (XVII).—A mixture of 3.0 g. of 2*H*-5,6-dihydropyranyl-3-acetic acid and 2 ml. of thionyl chloride was boiled under reflux for 40 min. The solution was diluted with benzene and then concentrated to remove excess thionyl chloride. This was repeated once more and then the residue was distilled to give 2.48 g. of the acid chloride as a colorless oil, b.p. 96–98° at 9 mm., $n^{20}D$ 1.5953. Since the acid chloride was somewhat unstable, it was treated directly with a solution of 1.90 g. of hexahydroindole[2] and 15 ml. of dry pyridine in 30 ml. of benzene. The resulting mixture was heated at 60–70° for 45 min. and then poured onto ice. The two layers were separated and the aqueous layer was extracted further with benzene. After the benzene extracts were washed successively with dilute acid, dilute base and water, they were concentrated to give 2.53 g. of a reddish oil. The infrared spectrum of this oil showed carbonyl absorption (5.87 μ) and lactam absorption (6.12 μ) as would be expected for the keto amide XVI. Since attempts to crystallize the oil were without success, it was purified by two successive short-path distillations. This gave 2.0 g. of an oil showing strong absorption at 6.00 (double bond) and at 6.12 μ (lactam). The composition of the distillate was in accord with that required for the cyclic enamide XVII.

Anal. Calcd. for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.25; H, 8.88; N, 5.83.

A solution of 2.0 g. of XVII in 125 g. of polyphosphoric acid was heated at 120–130° for 24 hr. under an atmosphere of nitrogen. The mixture then was poured onto ice, neutralized and extracted with chloroform. Concentration of the chloroform extracts gave a thick red oil which did not crystallize. Attempts to purify it by chromatography or distillation were unavailing. A portion of the oil was reduced directly with lithium aluminum hydride but the product, so obtained, did not form crystalline derivatives and showed an absorption band at 3.0 μ (N–H or –OH) in the infrared.

ROCHESTER, N. Y.

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

Synthesis of Potential Anticancer Agents. XIX. 2-Substituted N^6-Alkyladenines

BY JOHN A. MONTGOMERY, LEE B. HOLUM AND THOMAS P. JOHNSTON

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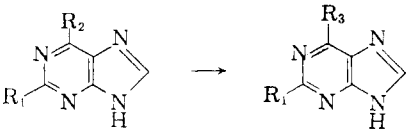
Several 2-substituted N^6-alkyladenines have been prepared from the corresponding 6-(alkylthio)-purines. Debenzylation of the N^6-alkyl-2-(benzylthio)-adenines has been effected by treatment with sodium in liquid ammonia.

Although a number of N^2-alkyl derivatives of guanine and 6-thioguanine have been prepared for screening as potential anticancer agents,[2] none of the isomeric derivatives of adenine has been reported, even though 6-amino-2-purinethiol, 2-(methylthio)-adenine and isoguanine have all shown some activity against Adenocarcinoma 755.[3] In order to investigate the possible anticancer activity of purines substituted in this manner, we have prepared some N^6-alkyladenines substituted in the 2-position by hydroxy, methylthio, benzylthio, and mercapto groups (Table I).

A number of $N^{2,6}$-alkyl derivatives of 2,6-diaminopurine, described in a previous paper of this series,[4] were obtained by stepwise aminations of 2,6-dichloropurine. Because acid hydrolysis of 2,6-dichloropurine gave xanthine, whereas basic hydrolysis gave 2-chloro-6-purinol,[5] one approach to the preparation of the 6-alkylamino-2-purinols IIa, b, c appeared to be acid hydrolysis of the corresponding N^6-alkyl-2-chloroadenines.[4] Although Davoll and Lowy[6] were able to obtain isoguanine



I II

Ia, R_1 = OH, R_2 = $SCH_2C_6H_5$
b, R_1 = R_2 = SCH_3
c, R_1 = R_2 = $SCH_2C_6H_5$
IIa, R_1 = OH, R_3 = $NHCH_3$
b, R_1 = OH, R_3 = $N(CH_3)_2$
c, R_1 = OH, R_3 = NH-*n*-C_4H_9
d, R_1 = SCH_3, R_3 = $NHCH_3$
e, R_1 = SCH_3, R_3 = NH-*n*-C_4H_9
f, R_1 = $SCH_2C_6H_5$, R_3 = $NHCH_3$
g, R_1 = $SCH_2C_6H_5$, R_3 = $N(CH_3)_2$
h, R_1 = $SCH_2C_6H_5$, R_3 = NH-*n*-C_4H_9

(1) Affiliated with Sloan-Kettering Institute. This work was supported by funds from the C. F. Kettering Foundation and the National Institutes of Health, Contract No. SA-43-ph-1740. Part XVIII, R. W. Balsiger, D. G. Jones and J. A. Montgomery, *J. Org. Chem.*, **24**, 434 (1959).

(2) G. B. Elion, W. H. Lange and G. H. Hitchings, THIS JOURNAL, **78**, 217 (1956).

(3) H. E. Skipper and J. R. Thomson, This Institute, private communication.

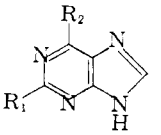
(4) J. A. Montgomery and L. B. Holum, THIS JOURNAL, **80**, 404 (1958).

(5) J. A. Montgomery and L. B. Holum, *ibid.*, **79**, 2185 (1957).

(6) J. Davoll and B. A. Lowy, *ibid.*, **74**, 1563 (1952).

TABLE I

2,6-DISUBSTITUTED PURINES



R_1	R_2	Crude yield, %	M.p., °C.	Recrystn. solvent[a]	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
OH	$SCH_2C_6H_5$	76	293–298 d.[b]	A	55.81	55.86	3.90	3.94	21.70	21.37
OH	$NHCH_3$	75	>300[b]	None	43.63	43.48	4.27	4.28	42.41	41.87
OH	$N(CH_3)_2$	85	>300[b]	B	46.92	46.86	5.06	5.38	39.09	38.81
OH	NH-*n*-C_4H_9	86	>300[b]	B	52.16	52.30	6.32	6.28	33.80	33.49
SCH_3	SCH_3	73[c]	260[d,e]	None	39.62	39.51	3.80	3.80	26.41	26.43
SCH_3	$NHCH_3$	75	>300[b]	None	43.07	43.40	4.65	4.78	35.89	35.72
SCH_3	$N(CH_3)_2$	84[f]	299[b,g]	[h]	45.93	46.07	5.30	5.36	33.48	33.27
SCH_3	NH-*n*-C_4H_9	38	254[d]	C	50.62	51.03	6.37	6.49	29.52	29.67
$SCH_2C_6H_5$	$SCH_2C_6H_5$	61	194–195[b]	D	62.63	62.23	4.43	4.42	15.38	15.39
$SCH_2C_6H_5$	$NHCH_3$	98	283–284[b]	D	57.56	57.73	4.83	4.66	25.82	25.45
$SCH_2C_6H_5$	$N(CH_3)_2$	92	270–270.5[b]	E	58.93	58.70	5.30	5.21	24.55	24.22
$SCH_2C_6H_5$	NH-*n*-C_4H_9	100	247–248[b]	D	61.32	61.32	6.11	5.98	22.35	22.07
SH	$NHCH_3$	73[i]	>300[b]	None	39.76	39.71	3.89	4.09	[j]	[j]
SH	$N(CH_3)_2$	71[i]	>300[b]	None	43.06	43.01	4.65	4.63	[k]	[k]
SH	NH-*n*-C_4H_9	69	272–277 d.[b]	None	48.42	48.05	5.87	5.74	31.38	31.58
NH_2	$SCH_2C_6H_5$	78	208[d]	None	56.02	55.72	4.31	4.28	27.23	26.90

[a] A, methyl Cellosolve; B, dimethylformamide; C, ethyl alcohol–water; D, ethyl alcohol; E, propyl alcohol. [b] Taken on Fisher–Johns apparatus. [c] Yield from final step of three-step sequence from 4-amino-2,6-dichloro-5-nitropyrimidine by the method of Dille and Christensen.[8] [d] Taken on Kofler Heizbank. [e] Lit.[5] m.p. 253–254°. [f] From cyclization of 4,5-diamino-6-dimethylamino-2-(methylthio)-pyrimidine (kindly supplied by American Cyanamid Co.) by the method of Baker, Joseph and Schaub.[12] Ring closure was also effected in 80% yield by heating 1.0 g. of the pyrimidine in 10 ml. of diethoxymethyl acetate at 120° for 1 hour. [g] Lit.[12] m.p. 284° (slight decompn.). [h] Purified by sublimation at 180–190° (0.06 mm.). [i] Based on an assumed monohydrate. The initially isolated hydrated compounds were dried *in vacuo* over phosphorus pentoxide at 110° for 40 hours in order to obtain anhydrous samples for analysis. [j] Calcd.: S, 17.69. Found: S, 17.58. [k] Calcd.: S, 16.42. Found: S, 16.24.

in moderate yield by the acid hydrolysis of 2-chloroadenine, we found that the N^6-alkyl-2-chloroadenines are resistant to hydrolytic attack and, in addition, isoguanine itself is apparently unstable in refluxing 20% hydrochloric acid. This stability of the C_2-chlorine was not surprising in view of the reported inertness of the methylthio group of 2-(methylthio)-adenine toward replacement by ammonia or amines[2,7] and the difficult replacement of the C_2-chlorine in N^6-alkyl-2-chloroadenines by amines.[4] That the nature of the group in the 6-position has a pronounced effect on the ease of replacement of the group in the 2-position has been demonstrated by Elion, Lange and Hitchings[2] by their successful aminations of 2-(methylthio)-6-purinol. The hydrolysis of the 2-chloroadenines was consequently abandoned in favor of the nucleophilic displacements Ia → IIa,b,c in which the benzylthio group in 6-(benzylthio)-2-purinol (Ia) was displaced to yield the desired 6-alkylamino-2-purinols IIa,b,c. Initially, 6-(methylthio)-2-purinol was considered an appropriate intermediate, but the attempted methylation of 6-mercapto-2-purinol in alkaline solution with dimethyl sulfate was unsuccessful, whereas benzylation with α-chlorotoluene under the same conditions worked well. The displacements were carried out with excess aqueous amines, diluted with either water or alcohol, in stainless steel bombs heated for 16 hours at 130° (for methyl- and dimethylamines diluted with alcohol) or for 20 hours at 110° (for butylamine diluted with water). The difficulty encountered due to the apparent instability of the basic solution of the product when exposed to air was overcome by immediate neutralization of the reaction mixture with acetic acid.[4]

The displacements Ib → IId,e were carried out on 2,6-bis-(methylthio)-purine (Ib), prepared initially from 4-amino-2,6-dichloro-5-nitropyrimidine by the method of Dille and Christensen,[8] but later by the $S^{2,6}$-dimethylation of commercially available[9] 2,6-purinedithiol in dimethylformamide—a procedure based on that previously used for the *S*-alkylation of 6-purinethiol.[10] The preferential displacement of the 6-(alkylthio) group is in accord with the previously observed difference in the ease of displacement of the C_2- and C_6-chlorines in 2,6-dichloropurine that made possible the isolation of N^6-alkyl-2-chloroadenines.[4] Thus, the reactions of methylamine and butylamine with 2,6-bis-(methylthio)-purine (Ib) produced the desired N^6-methyl-2-(methylthio)-adenine (IId) and N^6-butyl-2-(methylthio)-adenine (IIe), respectively. But failure to obtain an analytically pure product from the displacement with dimethylamine[11] prompted alternative preparations based on the

(7) K. J. M. Andrews N. Anand, A. R. Todd and A. Topham, *J. Chem. Soc.*, 2490 (1949).

(8) K. L. Dille and B. E. Christensen, THIS JOURNAL, **76**, 5087 (1954).

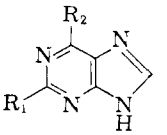
(9) Francis Earle Laboratories, 1057 Lower South St., Peekskill, N. Y.

(10) T. P. Johnston, L. B. Holum and J. A. Montgomery, THIS JOURNAL, **80**, 6265 (1958).

(11) 2,6-Bis-(methylthio)-purine (4.00 g.) in 10 ml. of 25% aqueous dimethylamine diluted to 100 ml., when heated at 150° for 16 hours in a stainless steel bomb, gave 1.86 g. (47%) of crude N^6,N^6-dimethyl-2-(methylthio)-adenine, m.p. 241–251° dec.; λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 256 (18.1), 290 (13.2); *p*H 7, 246 (19.2), 282 (12.0); *p*H 13, 237 (21.7), 291 (12.6).

TABLE II

ULTRAVIOLET ABSORPTION SPECTRA[a]



R_1	R_2	0.1 N HCl λ_{max}, mμ	0.1 N HCl ε × 10⁻³	pH 7 λ_{max}, mμ	pH 7 ε × 10⁻³	0.1 N NaOH λ_{max}, mμ	0.1 N NaOH ε × 10⁻³
OH	$SCH_2C_6H_5$			266	7.68	322	11.5
				317	13.4		
OH	$NHCH_3$	285–286	14.0	241	9.33	285	13.9
				281	11.4		
OH	$N(CH_3)_2$	289	15.1	249	10.2	284	12.2
				284	12.2		
OH	NH-*n*-C_4H_9	287	15.5	242	9.55	286	14.5
				286	14.5		
SCH_3	SCH_3	261	18.8	226	14.6	244	22.8
		313	10.2	257	19.8	310	10.9
				306	10.7		
SCH_3	$NHCH_3$	249	17.1	239	21.7	230	25.0
		288	13.7	278	14.0	284	13.5
SCH_3	$N(CH_3)_2$	253	19.7	245	23.6	236	24.8
		292	16.3	283	15.5	290	14.3
SCH_3	NH-*n*-C_4H_9	251	19.7	241	22.9	284	14.7
		289	16.0	279	15.2		
$SCH_2C_6H_5$	$SCH_2C_6H_5$			260[b]	23.0	247	22.1
				311[b]	12.0	312	12.1
$SCH_2C_6H_5$	$NHCH_3$	252	18.2	240	21.4	285	14.2
		289	15.2	280	14.8		
$SCH_2C_6H_5$	$N(CH_3)_2$	256	19.4			292	15.2
		292	16.6				
$SCH_2C_6H_5$	NH-*n*-C_4H_9	254	18.5	240[b]	25.8	287	15.5
		290	16.1	283[b]	15.8		
SH	$NHCH_3$	245	16.1	261	17.5	241–242	19.5
		287	18.5			282	11.0
SH	$N(CH_3)_2$	255	16.0	269	20.1	252	20.2
		288	19.8			290	12.5
SH	NH-*n*-C_4H_9	248	15.4	266	16.5	238	19.4
		286	18.2			283	13.0
NH_2	$SCH_2C_6H_5$	276	9.80	242	12.4	226	21.8
		318	14.9	310	11.9	315	11.4

[a] Determined with a Beckman model DK-2 spectrophotometer; optical densities at the maxima measured with a Beckman model DU spectrophotometer. [b] In ethyl alcohol.

previously reported[12] cyclization of 4,5-diamino-6-dimethylamino-2-(methylthio)-pyrimidine to the desired N^6,N^6-dimethyl-2-(methylthio)-adenine. Ring closure was effected by treatment of the pyrimidine with either diethoxymethyl acetate[4] or formic acid followed by formamide.[12]

The attempted conversion of the available N^6-alkyl-2-chloroadenines[4] to the corresponding N^6-alkylamino-2-purinethiols by treatment of the 2-chloroadenines with thiourea, even in boiling ethylene glycol, was unsuccessful; only unchanged starting material was recovered. This result is in contrast to the preparation of 2,6-dichloropurine with thiourea in boiling ethyl alcohol.[13] However, a convenient synthesis of the 6-alkylamino-2-purinethiols of Table I was afforded by the debenzylation of the N^6-alkyl-2-(benzylthio)-adenines IIf,g,h by the action of sodium in liquid ammonia.[14]

The preparations of the title purines as well as some of the starting materials and the related 2-amino-6-(benzylthio)-purine are summarized in Table I. Examples of typical procedures employed are given in the Experimental section. The ultraviolet absorption spectra of analytically pure samples of the purines listed in Table I are recorded in Table II.

An unequivocal structural assignment for the N^6-alkyl-2-(alkylthio)-adenines IId,e,f,g,h that were derived by nucleophilic displacements on the corresponding 2,6-bis-(alkylthio)-purines Ib,c is provided by a comparison of their ultraviolet absorption spectra with the spectra of N^6,N^6-dimethyl-2-(methylthio)-adenine obtained by ring closure of the corresponding 4,5-diaminopyrimidine. The marked dissimilarity observed when the spectra of the N^6-alkyl-2-(alkylthio)-adenines are compared with the spectra of 2-amino-6-(benzylthio)-purine (Table II) may be cited as corroborative evidence that the structural assignments are correct. Fur-

(12) B. R. Baker, J. P. Joseph and R. E. Schaub, *J. Org. Chem.*, **19**, 631 (1954).

(13) G. H. Hitchings and G. B. Elion, U. S. Patent 2,697,709 (Dec. 21, 1954).

(14) See W. H. Hartung and R. Simonoff in "Organic Reactions," Vol. VII, John Wiley and Sons, Inc., New York, N. Y., 1953, pp. 280–281.

thermore, distinct spectral differences obtain in the spectra of other 2(6),6(2)-disubstituted purine pairs such as the 6-alkylamino-2-purinols and 6-alkyl amino-2-purinethiols of Table II *versus* the corresponding isomers reported by Elion, Lange and Hitchings.[2] The $S^{2,6}$-dialkylation of 2,6-purinedithiol appears to produce hypsochromic shifts of the major maxima in the spectra of the resulting 2,6-bis-(alkylthio)-purines, as does the *S*-methylation of 2-mercapto-6-purinol[2] and the *S*-benzylation of 6-mercapto-2-purinol in the spectra of the respective products, 2-(methylthio)-6-purinol[2] and 6-(benzylthio)-2-purinol (Ia).

Acknowledgment.—The authors are indebted to Mr. J. P. Holmquist and Mr. J. W. Murphy for most of the microanalytical results reported, to Mr. L. D. Norton for the spectral determinations, and to Miss Anne Gallagher and Mr. B. B. Thompson for technical assistance. Some of the analyses reported were performed by the Galbraith Microanalytical Laboratories, Knoxville, Tenn.

Experimental

6-(Benzylthio)-2-purinol (Ia).—α-Chlorotoluene (0.35 ml., 3.0 mmoles) was added with vigorous stirring to a solution of 500 mg. (3.00 mmoles) of 6-mercapto-2-purinol[9] in 3.0 ml. of 1 *N* aqueous sodium hydroxide diluted to 35 ml. with water. A light-tan solid precipitated immediately after the addition was completed. Stirring was continued for an hour, and the solid was collected by filtration, washed with water and ethyl alcohol, and dried *in vacuo* over phosphorus pentoxide at 110°; yield 590 mg. (72%), m.p. 293–298° dec. Recrystallization of a 460-mg. sample from 50 ml. of methyl Cellosolve gave a 57% recovery of an analytically pure sample, analytical and spectral data for which are recorded in Tables I and II, respectively. A subsequent run in which 0.18 mole of starting materials was used gave a 90% yield of recrystallized product.

6-Dimethylamino-2-purinol (IIb).—A solution of 6.00 g. (23.2 mmoles) of 6-(benzylthio)-2-purinol (Ia) in 25 ml. of a 25% aqueous solution of dimethylamine diluted to 150 ml. with ethyl alcohol was heated at 130° for 16 hours in two 100-ml. stainless steel bombs. The bombs then were chilled and opened, and the contents neutralized with acetic acid. The resulting white solid was collected by filtration, washed with water and ethyl alcohol, and air-dried; weight 2.99 g., m.p. >300°. Two additional crops of less pure material totaling 0.52 g. were obtained from the concentrated filtrate; total yield 84.5%. Recrystallization of a small amount from dimethylformamide gave an analytically pure sample, analytical and spectral data for which are recorded in Tables I and II, respectively.

6-Butylamino-2-purinol (IIc).—A solution of 5.00 g. (19.4 mmoles) of 6-(benzylthio)-2-purinol (Ia) in 100 ml. of a 10% aqueous solution of butylamine heated for 20 hours at 110° in two 100-ml. stainless steel bombs. The bombs then were chilled and opened, and the contents immediately neutralized to *p*H 6 with acetic acid. The white solid that precipitated was collected by filtration, washed with water and ethyl alcohol, and dried *in vacuo* over phosphorus pentoxide; yield 3.47 g. (86%), m.p. >300°. The analytically pure sample (Table I) was obtained by recrystallization of a small portion of the above crude product from dimethylformamide; ultraviolet spectral data are recorded in Table II.

2,6-Bis-(methylthio)-purine (Ib).—Iodomethane (1.4 ml., 22 mmoles) was added to a well-stirred mixture of 1.90 g. (10.3 mmoles) of 2,6-purinedithiol,[9] 2.85 g. (20.6 mmoles) of anhydrous potassium carbonate and 15 ml. of dimethylformamide at room temperature (*ca.* 25°). The temperature of the reaction mixture rose to about 40° within 4 minutes and then began to fall. Stirring was continued for 30 minutes, following which the reaction mixture was poured into 100 ml. of water and acidified with acetic acid. The mixture was refrigerated, and the precipitated solid was collected by filtration, washed with water, and air-dried; yield 1.66 g. (76%), m.p. 256°. The ultraviolet absorption spectra indicated that this material was sufficiently pure for use as an intermediate in subsequent displacement reactions.

N^6-Methyl-2-(methylthio)-adenine (IId).—A solution of 925 mg. (4.36 mmoles) of 2,6-bis-(methylthio)-purine (Ib) in 50 ml. of a 20% aqueous solution of methylamine was heated at 130° for 16 hours in a 100-ml. stainless steel bomb. Acidification of the orange solution with glacial acetic acid resulted in the separation of a light cream-colored solid. After the mixture was chilled, the solid was collected by filtration, washed with water, and dried *in vacuo* at 110° over phosphorus pentoxide; yield 640 mg. (75%), m.p. >300°. The analytical and spectral data are recorded, respectively, in Tables I and II.

2,6-Bis-(benzylthio)-purine (Ic).—A solution of 2.50 g. (13.6 mmoles) of 2,6-purinedithiol[9] in 25.4 ml. of 1.07 *N* aqueous sodium hydroxide was diluted to 100 ml. with water, and 3.14 ml. (27.2 mmoles) of α-chlorotoluene was added with vigorous stirring. Stirring was continued for 2 hours, during which period a solid slowly precipitated. The mixture was chilled, and the solid was collected by filtration, washed with water, and air-dried; yield 3.00 g. (61%) of a cream-colored powder, m.p. 192–193°. Recrystallization from 200 ml. of ethyl alcohol gave 2.50 g. of analytically pure material, physical data for which are recorded in Tables I and II.

A subsequent dibenzylation was carried out in dimethylformamide by a procedure similar to that described for the preparation of Ib. A 94% yield of unrecrystallized product, m.p. 195°, was obtained from 5.00 g. of 2,6-purinedithiol, the ultraviolet absorption spectra of which compared favorably with those of the analytically pure sample.

2-(Benzylthio)-N^6-butyladenine (IIh).—A solution of 500 mg. (1.37 mmoles) of 2,6-bis-(benzylthio)-purine (Ic) in 5 ml. of butylamine diluted to 10 ml. with water was heated at 130° for 16 hours in a 20-ml. stainless steel bomb. After being chilled in ice, the bomb was opened and the excess butylamine was neutralized with glacial acetic acid. The light-green solid that precipitated was collected by filtration, washed thoroughly with water, and air-dried; crude yield 430 mg. (100%), m.p. 241–246° dec. Recrystallization of the above crude material from 25 ml. of ethyl alcohol gave 200 mg. of yellow crystals, m.p. 247–248°, the analytical and spectral data for which are given in Tables I and II, respectively.

In subsequent larger runs it was found advantageous to displace the air in the bombs with nitrogen before sealing and to keep the reaction mixture cool and under nitrogen during the neutralization step. Thus, a mixture of 8.0 g. of 2,6-bis-(benzylthio)-purine and 50 ml. of butylamine diluted to 100 ml. with water and heated at 130° for 16 hours gave, after recrystallization from ethyl alcohol with Norit treatment, 3.0 g. (44%) of pale yellowish-green crystals, which melted at 232.5°, then resolidified and remelted at 250° (Kofler Heizbank); λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 254 (19.6), 291 (17.1); *p*H 13, 287 (15.5); EtOH, 240–241 (25.5), 280 (16.4).

6-Butylamino-2-purinethiol.—Metallic sodium was added in small increments to a solution of 1.00 g. (3.20 mmoles) of 2-(benzylthio)-N^6-butyladenine (IIh) in 100 ml. of liquid ammonia, a total of 470 mg. (20.5 mmoles) of sodium being required to give a blue color that lasted more than 10 minutes. A small amount of ammonium chloride was added to clarify the solution, and then the ammonia was allowed to evaporate to a small volume. Ethyl ether (100 ml.) was added, and the mixture was warmed cautiously until frothing had subsided and the evolution of ammonia had nearly ceased. The mixture then was extracted with water (3 × 100 ml.). The combined aqueous extracts were filtered and the filtrate acidified with acetic acid, a light-tan solid being precipitated. The mixture was refrigerated overnight, and the solid was collected by filtration, washed with water, and air-dried; yield 490 mg. of anhydrous[15] powder (69%), dec. 272–277°; the analytical and spectral data are given in Tables I and II, respectively. A monohydrate of this compound was obtained by the following procedure. A small sample in dilute aqueous sodium hydroxide containing a pinch of Norit was brought quickly to

(15) In contrast, the 6-methylamino and 6-dimethylamino analogs isolated similarly, and even dried *in vacuo* over phosphorus pentoxide at room temperature for 24 hours, were hydrated compounds; anhydrous samples were obtained by force-drying *in vacuo* at 110°.

boiling, then cooled immediately and filtered. The filtrate was acidified to *p*H 4–5 with 6 *N* hydrochloric acid and the resulting pale cream-colored precipitate was collected, washed with water, and dried *in vacuo* over phosphorus pentoxide at room temperature; λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 247–248 (15.0), 285 (17.5); *p*H 7, 267 (16.2); *p*H 13, 237–238 (18.4), 283–284 (13.0).

Anal. Calcd. for $C_9H_{13}N_5S \cdot H_2O$: C, 44.80; H, 6.27. Found: C, 44.84; H, 6.28.

2-Amino-6-(benzylthio)-purine.—A solution of 500 mg. (3.00 mmoles) of 2-amino-6-purinethiol[9] in 2.8 ml. of 1.07 *N* aqueous sodium hydroxide diluted to 30 ml. with water was treated, while stirred vigorously, with 0.35 ml. (3.0 mmoles) of α-chlorotoluene. A white solid precipitated within 5 minutes after the addition was completed, and stirring was continued for 2 hours to ensure complete reaction. The mixture then was chilled and the solid collected by filtration, washed with water and ethyl alcohol, and dried *in vacuo* over phosphorus pentoxide at 110°; yield 600 mg. (78%), m.p. 208°. The analytical and spectral data are recorded in Tables I and II, respectively.

In a later run in which dimethylformamide and potassium carbonate were used—according to a procedure similar to that described for Ib except that the mixture was heated between 50 and 60° for 30 minutes—a 94% yield of 2-amino-6-(benzylthio)-purine, m.p. 210°, was obtained; λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 277 (9.35), 320 (13.9); *p*H 7, 243 (11.4), 313 (11.5); *p*H 13, 316 (10.9).

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[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL SCIENCES, STANFORD RESEARCH INSTITUTE]

Potential Anticancer Agents.[1] XIX. Synthesis of 2′-Deoxyadenosine[2]

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The first synthesis of a naturally occurring purine 2′-deoxynucleoside has been achieved. The key reaction is an ethylthio migration from C.3′ to C.2′ based on the selectivity of nucleophilic attack on a nucleoside 2′,3′-episulfonium ion. This method should be adaptable to the synthesis of the 2′-deoxyribofuranosyl derivatives of both natural and unnatural bases and to the preparation of analogs of natural deoxynucleosides modified at C.3′. It therefore provides a route to two classes of potential deoxynucleoside antagonists that might exhibit anticancer activity.

The syntheses of the four nucleosides obtained on hydrolysis of ribonucleic acids, accomplished by Todd and his co-workers, were published in 1947 and 1948.[3] However, the first synthesis of a 2′-deoxyribofuranosylnucleoside, 2′-deoxyuridine, was announced only slightly more than a year ago.[4] Shortly afterward the synthesis of the first component of deoxynucleic acids, the pyrimidine 2′-deoxyribonucleoside thymidine, was reported by Shaw and Warrener.[5,6] In addition, a number of enzymatic syntheses of unnatural 2′-deoxynucleosides have appeared over the last few years.[7]

It was pointed out when this work was undertaken[8] that the then known chemical methods were inadequate for the preparation of 2′-deoxynucleosides. Davoll, Lythgoe and Trippett,[9] for instance, attempted to obtain 2′-deoxynucleosides from two 2′,3′-anhydrofuranosyl nucleosides by reaction with sodium ethyl mercaptide and subsequent desulfurization. Unfortunately, their method failed because the mercaptide ion attacked the anhydronucleosides almost exclusively at C.3′. This phenomenon of very predominant attack on 2,3-anhydro ribo- or lyxofuranosides at C.3 has been observed in all the additional cases that have been studied.[10] On the assumption that a 2,3-episulfonium ion, in its reactions with nucleophiles, would show a selectivity similar to that which is exhibited by 2,3-anhydrofuranosides, the suggestion was made that it should be possible to isomerize a 3′-alkylthio nucleoside having a *trans*-2′-hydroxyl group to a 2′-alkylthio nucleoside *via* the related 2′,3′-episulfonium ion.[8] That such an isomerization is indeed possible was first demonstrated in the methyl furanoside series.[11] Use of such an alkylthio migration has now made possible the first chemical synthesis of a naturally occurring purine 2′-deoxynucleoside, namely, 2′-deoxyadenosine (XI). The procedure employed is the first completely general method for the chemical synthesis of 2′-deoxynucleosides since the earlier deoxynucleoside syntheses[4,5] were dependent on activation of a C.2′ leaving group by a neighboring 2-oxo- or 2-thiopyrimidine moiety.

The starting material for the synthesis of 2′-deoxyadenosine (XI) was 1,2-di-*O*-acetyl-5-*O*-methoxycarbonyl-3-*O*-(*p*-tolylsulfonyl)-D-xylofuranose (I), an intermediate employed earlier in a synthesis of the methyl 2,3-anhydro-D-ribofuranosides[12]; the over-all yield of XI from I was 0.5%. The diacetate I was treated with ethereal hydrogen chlo-

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center of the National Cancer Institute, Contract No. SA-43-ph-1892. For the preceding paper of this series, *cf.* M. H. Gram, C. W. Mosher and B. R. Baker, THIS JOURNAL, **81**, 3103 (1959).

(2) For a preliminary announcement of this synthesis, see C. D. Anderson, L. Goodman and B. R. Baker, THIS JOURNAL, **80**, 6453 (1958).

(3) For reviews of this work, see G. W. Kenner, *Fortschr. Chem. org. Naturstoffe*, **8**, 96 (1951), and J. Baddiley in "Nucleic Acids," Vol. I, ed. by E. Chargaff and J. M. Davidson, Academic Press, Inc., New York, N. Y., 1955, p. 137.

(4) (a) D. M. Brown, D. B. Parihar, C. B. Reese and A. Todd, *Proc. Chem. Soc.*, 321 (1957); (b) *J. Chem. Soc.*, 3035 (1958); (c) D. M. Brown, D. B. Parihar and A. Todd, *ibid.*, 4242 (1958).

(5) G. Shaw and R. N. Warrener, *Proc. Chem. Soc.*, 81 (1958).

(6) An alternative synthesis of thymidine was reported by Brown, *et al.*, in the same paper in which they detailed the synthesis of 2′-deoxyuridine (see ref. 4b).

(7) *E.g.*, M. Friedkin, *Biochim. et Biophys. Acta*, **18**, 447 (1955); W. H. Prusoff, *J. Biol. Chem.*, **215**, 809 (1955); R. H. Hall and R. Hazelkorn, THIS JOURNAL, **80**, 1138 (1958); C. Heidelberger, L. Griesbach, O. Cruz, R. J. Schnitzer and E. Grunberg, *Proc. Soc. Exp. Biol. Med.*, **97**, 470 (1958).

(8) L. Goodman, A. Benitez and B. R. Baker, Paper I of this series, THIS JOURNAL, **80**, 1680 (1958).

(9) J. Davoll, B. Lythgoe and S. Trippett, *J. Chem. Soc.*, 2230 (1951).

(10) For further discussion of this point, see ref. 11 and R. E. Schaub and M. J. Weiss, THIS JOURNAL, **80**, 4683 (1958).

(11) C. D. Anderson, L. Goodman and B. R. Baker, Paper XVI of this series, *ibid.*, **81**, 898 (1959).

(12) C. D. Anderson, L. Goodman and B. R. Baker, Paper VII of this series, *ibid.*, **80**, 5247 (1958).