Table I. Isotopic Distribution of Molecular Oxygen Evolved during the Self-Reactions of Some Peroxy Radicals

Peroxy radical	Relative yields of oxygen, %[a] $^{32}O_2$	$^{34}O_2$	$^{36}O_2$
2-Propyl	43	14	43
1-Butyl	47	6	47
2-Butyl	29	42	29
tert-Butyl	44	12	44
Cyclopentyl	29	42	29
Acetyl	29	42	29
2-Pyridyl	37	26	37

[a] Yields of $^{32}O_2$ and $^{36}O_2$ corrected to allow for departures from 1:1 ratio in original oxygen mixture.

For *tert*-butylperoxy radicals (which gave a particularly low ratio of scrambled to unscrambled oxygen) it was possible to prepare a mixture of t-Bu^{16}O^{16}O· and t-Bu^{18}O^{13}O· in the liquid phase by photolysis of a mixture of di-*tert*-butyl peroxide and isobutane in the presence of $^{32}O_2$ and $^{36}O_2$. This radical was quite stable below −100° and the solution could be thoroughly degassed between −196 and −100° without the loss of a significant fraction of the radicals. Thus the unreacted oxygen could be removed completely from the system. When this sample was warmed to a temperature at which the radicals underwent self-reaction, the oxygen evolved was scrambled statistically (25:50:25). This result would appear to confirm our suspicion that the low yields of $^{34}O_2$ observed for some of the radicals (Table I) were caused by unreacted oxygen trapped in the matrix.

The detection of $^{34}O_2$ from the self-reaction of primary, secondary, and tertiary alkylperoxy radicals in this work provides further evidence that the transition state for this reaction involves a head-to-head interaction between two radicals. The results also show that a similar interaction occurs for the acetylperoxy and 2-pyridylperoxy radicals, and thus it probably occurs for organic peroxy radicals in general.

Acknowledgment. We thank Messrs. C. P. Rimmer and R. Summers for assistance with the experimental work.

Controlled Interaction between Nucleic Acid Bases. Intramolecular Stacking Interactions between Two Adenine Rings[1-3]

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Abstract: In order to determine the stacking interactions between two parallel adenine rings oriented at different axis angles toward each other, we have synthesized a series of six different trimethylenebisadenine isomers. The per cent hypochromism, H, for the long wavelength ultraviolet absorption band for each of these compounds has been determined by comparison of the ultraviolet spectrum of the trimethylenebisadenine in aqueous solution with the composite spectrum of the two "half" molecules, the appropriate propyladenines. The H values obtained thereby for the trimethylenebisadenines are the following: 9,9′ isomer, 15%; N^6,N$^{6'}$, 16%; 8.8′, 21%; N^6, 9′, 16%; 8,9′, 19%; 7,9′, 16%. The per cent hypochromism follows a dependence upon the folded conformations available to the individual trimethylenebisadenines and offers the possibility of assessing the degree and orientation of overlap permitted or excluded for different ranges of H values.

In 1954 we described the use of the trimethylene bridge, $-(CH_2)_3-$, as a synthetic spacer in the construction of compounds for the detection of intramolecular interaction between electron-donating and electron-accepting groups.[4] Later, we used the trimethylene bridge as a synthetic spacer to simulate intramolecular interactions between nucleic acid bases, as in B-$(CH_2)_3$-B, and between the component heterocyclic rings of certain coenzymes in aqueous solution.[5,6] We considered that this chain length was particularly advantageous in permitting nearly plane-parallel stacking of the rings, a feature that was verified in aqueous solution by ultraviolet hypochromism,[6] in an ethylene glycol–water glass at low temperature by the emission spectral characteristics,[6] and in the crystal, for the case of 1,1′-trimethylenebisthymine, by the X-ray structure analysis.[7-11]

(1) This work was supported by Research Grant No. USPHS-GM-05829 from the National Institutes of Health, U. S. Public Health Service.

(2) The present paper is no. XII in the series on Synthetic Spectroscopic Models Related to Coenzymes and Base Pairs.

(3) For the preceding paper (XI) in this series, see N. J. Leonard, R. S. McCredie, M. W. Logue, and R. L. Cundall, *J. Amer. Chem. Soc.*, **95**, 2320 (1973); see references therein.

(4) N. J. Leonard, R. C. Fox, M. Ōki, and S. Chiavarelli, *ibid.*, 76, 630 (1954).

(5) N. J. Leonard, T. G. Scott, and P. C. Huang, *ibid.*, **89**, 7137 (1967).

(6) D. T. Browne, J. Eisinger, and N. J. Leonard, *ibid.*, **90**, 7302 (1968).

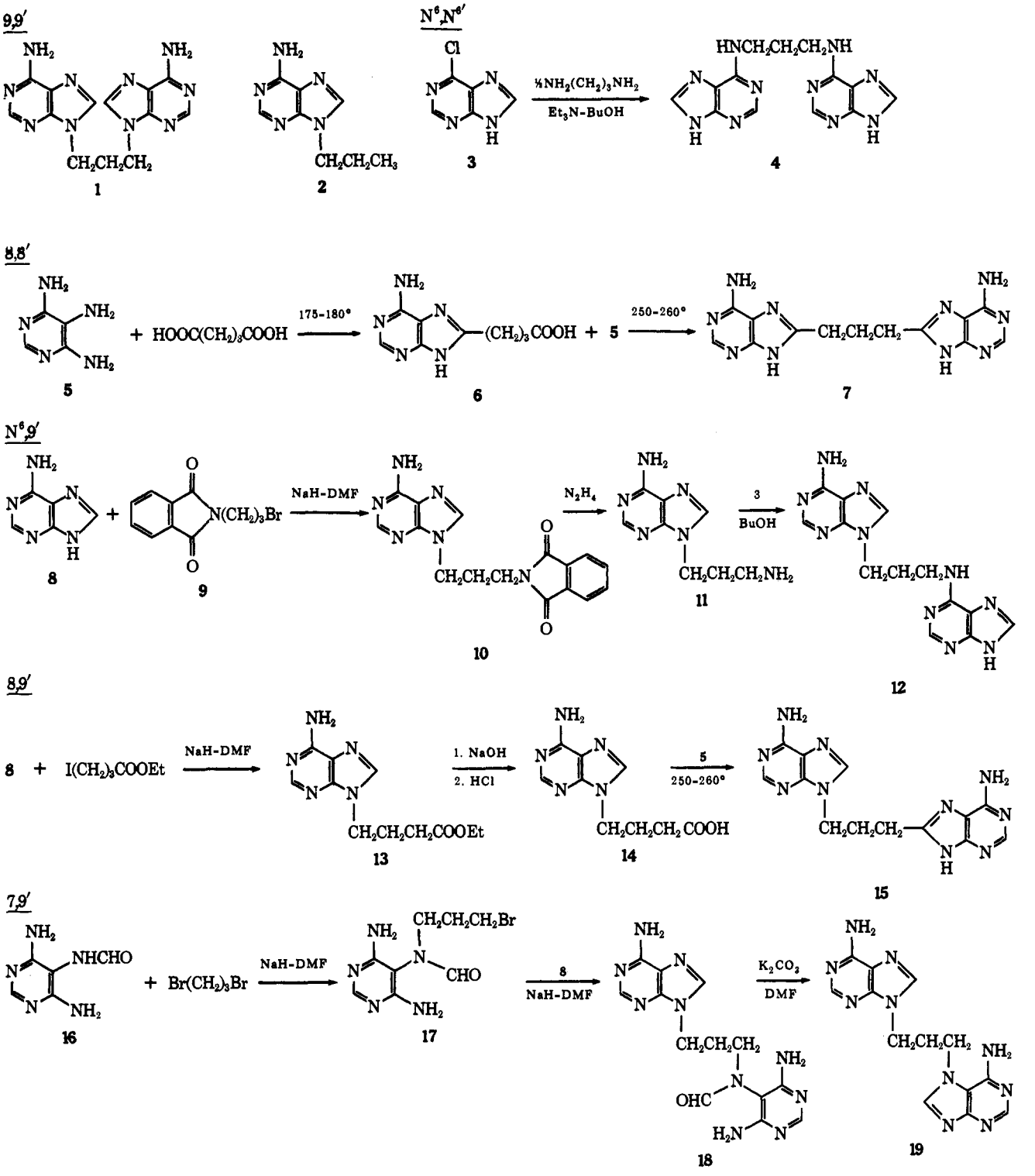
(7) J. K. Frank and I. C. Paul, *ibid.*, **95**, 2324 (1973).

(8) For similar stacking of rings in another trimethylene-bridged compound, 8,8′-trimethylenebistheophylline, as determined by X-ray structure analysis, see L. S. Rosen and A. Hybl, *Acta Crystallogr., Sect. B*, 27, 952 (1971).

(9) The geometry for the case of two slightly deformed benzene rings held nearly plane parallel by two trimethylene bridges is described in the X-ray structure of [3,3]paracyclophane; see P. K. Gantzel and K. N. Trueblood, *ibid.*, **18**, 958 (1965); also D. J. Cram, N. L. Allinger, and H. Steinberg, *J. Amer. Chem. Soc.*, 76, 6132 (1954); D. J. Cram and R. H. Bauer, *ibid.*, **81**, 5971 (1959); D. J. Cram and H. Steinberg, *ibid.*, **73**, 5691 (1951).

(10) The X-ray structure of janusene provides a case in which two benzene rings are held slightly tilted away from the plane-parallel arrangement, at interatomic distances 3.1–4.0 Å: see S. J. Cristol and

Scheme I



The trimethylene bridge also provides the possibility of controlling the inter-ring interaction to some extent by attachment of the chain to different positions on the heterocyclic termini. For example, the folded or stacked conformations available to 9,9′-trimethylenebisadenine,[6] Ade-C_3-Ade or Ade^9-C_3-Ade^9 (**1**),[12] as described by the angle between the ring axes 4,5 and 4′,5′, are limited by the positions of attachment 9 and 9′. We have now synthesized five other trimethylenebisadenine isomers having different positions of attachment to the terminal adenines and therefore having differently oriented ring axes permissible in their stacked conformations. In this article, we report the synthetic methodology and the relative hypochromisms of the long wavelength band in the

D. C. Lewis, *ibid.*, **89**, 1476 (1967); S. J. Cristol and W. Y. Lim, *J. Org. Chem.*, **34**, 1 (1969).

(11) F. Hirayama, *J. Chem. Phys.*, **42**, 3163 (1965), has shown in the series $Ph(CH_2)_nPh$ that aromatic ring interaction is uniquely favored when $n = 3$.

(12) The three-letter abbreviation is preferred over Ad,[5,6] and the superscript indicates the point of attachment; for example, Ade^6-C_3-Ade^9 is N^6,9′-trimethylenebisadenine and Ade^8-C_3-Ade^9 is 8,9′-trimethylenebisadenine.

ultraviolet absorption spectra, and in the collaborative sequel[13] we report the magnetic circular dichroism for the series of isomers.

Synthesis

In order to determine the per cent hypochromisms,[5,6,14-17] for the individual trimethylenebisadenines in the series, it was necessary to synthesize the corresponding half-molecules, such as Ade^9-C$_3$ (**2**) as well. These either had been synthesized earlier or could be made by standard methods. Among the trimethylenebisadenines, the 9,9′ isomer (**1**) was described earlier from this laboratory, and the corresponding ethylene and hexamethylene homologs were made earlier by Lister.[18] N^6,$N^{6'}$-Trimethylenebisadenine, Ade^6-C$_3$-Ade^6 (**4**) (or 6,6′(-trimethylenediamino)bispurine), which was prepared by the condensation of 1,3-diaminopropane with 2 molar equiv of 6-chloropurine (**3**), was converted to the bispicrate for comparison with this derivative previously described.[19] 8,8′-Trimethylenebisadenine, Ade^8-C$_3$-Ade^8 (**7**), was prepared from glutaric acid and 4,5,6-triaminopyrimidine (**5**) in stages, proceeding through 4-(aden-8-yl)butyric acid (**6**). N^6,9′-Trimethylenebisadenine, Ade^6-C$_3$-Ade^9 (**12**), was prepared starting with the alkylation of adenine (**8**) with *N*-(3-bromopropyl)phthalimide (**9**) to give 9-(3-phthalimidopropyl)adenine (**10**), followed by hydrazinolysis to 9-(3-aminopropyl)adenine (**11**)[20] and then condensation with 6-chloropurine (**3**), (Scheme I). 8,9′-Trimethylenebisadenine, Ade^8-C$_3$-Ade^9 (**15**), was synthesized *via* 9-alkylation of adenine with ethyl 4-iodobutyrate to give ethyl 4-(aden-9-yl)butyrate (**13**), saponification to 4-(aden-9-yl)butyric acid (**14**), and condensation with 4,5,6-triaminopyrimidine (**5**). The synthesis of 7,9′-trimethylenebisadenine, Ade^7-C$_3$-Ade^9 (**19**), started with the alkylation of 4,6-diamino-5-formylaminopyrimidine (**16**) with 1,3-dibromopropane according to the method of Denayer, Cavé, and Goutarel[21] for the preparation of 7-substituted adenines. The intermediate 5-*N*-(3-bromopropyl)formylamino-4,6-diaminopyrimidine (**17**) was then employed in the 9-alkylation of adenine, and the resulting 5-*N*-[3-(aden-9-yl)propyl]formylamino-4,6-diaminopyrimidine (**18**) was heated with anhydrous potassium carbonate in dimethylformamide for the final ring closure. The identity of each trimethylenebisadenine was indicated by the path of synthesis and confirmed by the proton magnetic resonance spectrum. The purity of each trimethylenebisadenine and propyladenine was established by microanalysis, mass spectrometry, and thin layer chromatography using four different solvent systems.

(13) E. Bunnenberg, C. Djerassi, K. Mutai, and N. J. Leonard, in preparation.
(14) I. Tinoco, Jr., *J. Amer. Chem. Soc.*, **82**, 4785 (1960); **83**, 5047 (1961).
(15) I. Tinoco, Jr., *J. Chem. Phys.*, **33**, 1332 (1960); **34**, 1067 (1961).
(16) N. J. Leonard, H. Iwamura, and J. Eisinger, *Proc. Nat. Acad. Sci., U. S.*, **64**, 352 (1969).
(17) H. Iwamura, N. J. Leonard, and J. Eisinger, *ibid.*, **65**, 1025 (1970).
(18) J. H. Lister, *J. Chem. Soc.*, 3394 (1960).
(19) (a) H. Lettré and H. Ballweg, *Naturwissenschaften*, **45**, 364 (1958); (b) *Justus Liebigs Ann. Chem.*, **649**, 124 (1961).
(20) (a) N. J. Leonard and R. F. Lambert, *J. Org. Chem.*, **34**, 3240 (1969); (b) J. H. Lister, *J. Chem. Soc.*, 3682 (1960), first made Ade^6-C$_2$-Ade^9 in this series.
(21) (a) R. Denayer, A. Cavé, and R. Goutarel, *C. R. Acad. Sci.*, **253**, 2994 (1961); (b) R. Denayer, *Bull. Soc. Chim. Fr.*, 1358 (1962).

Hypochromism

The ultraviolet absorption spectra of the trimethylenebisadenines and the corresponding "half" molecules, the propyladenines, were determined in aqueous solution at concentrations low enough to avoid intermolecular association so that perturbations associated with the 1:1 interaction between a pair of adenines within the same molecule alone would be detected. A meaningful criterion for assessing interaction has been shown to be the per cent hypochromism, H,[14,15,22] which corresponds to an integrated hypochromic effect and is usually calculated for the long wavelength band in dinucleoside phosphates[23] and their models.[6,16,17] In such series, the dinucleotide or model exhibits substantially reduced absorption compared with that of its constituent monomeric or half units. Hypochromism is defined in terms of the oscillator strengths, f, which in our study have been determined by computer integration of the absorption curves, using intervals of 2.5 nm, beginning in the vicinity of the first-absorption minimum. Calculation of per cent hypochromism is then carried out by substitution of the oscillator strengths in the equation $H = [1 - f_{AB}/(f_A + f_B)]100$, where f_A and f_B are the oscillator strengths of the appropriate propyladenines and f_{AB} is the oscillator strength of the trimethylenebisadenine; *e.g.*, for AB = **15**, A = 9-propyladenine and B = 8-propyladenine. The values of H for the six trimethyleneadenines here studied are given in Table I as computed for neutral aqueous solution at 25°. Based on the earlier study[6] which included Ade^9-C$_3$-Ade^9, the values of H for acidic aqueous solutions can safely be predicted to be very small as compared with those obtained under neutral conditions. The hypochromism vanishes in ethanol solution.[6]

Table I. Computed Per Cent Hypochromism, H, for Isomeric Trimethylenebisadenines

Compd	Ade-C$_3$-Ade isomer	H,[a] %
1	9,9′	14.8[b]
4	N^6,$N^{6'}$	15.5 (17.6)[c]
7	8,8′	21.2
12	N^6,9′	16.5 (16.9)[d]
15	8,9′	19.2
19	7,9′	16.0

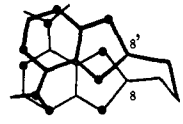
[a] Aqueous, neutral solution at 25°. These values are considered reproducible to ±0.5. [b] This value is refined over that previously reported for **I** and represents part of a careful study of the influence of temperature and of chain length on H by Charlotte Otto in this laboratory. [c] The figure 15.5 is computed on the basis of 6-propylaminopurine as the half molecule; 17.6, on 6-(3-aminopropylamino)purine (in 0.05 *M* phosphate buffer). [d] The figure 16.5 is computed on the basis of Ade^6-C$_3$ and Ade^9-C$_3$ as halves; 16.9, on Ade^6-C$_3$ and Ade^9-C$_3$-NH$_2$.

One of the striking features in the list of H values presented in Table I is the clustering of four of the values around 15.65 ± 0.85. Thus, the percentages of hypochromism calculated for the 9,9′-, N^6,$N^{6'}$-, N^6,9′-, and 7,9′-trimethylenebisadenines are not appreciably different and are indicative of strong intramolecular interaction between the trimethylene-separated adenines in each case, corresponding to folded

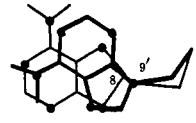
(22) W. Rhodes, *J. Amer. Chem. Soc.*, **83**, 3609 (1961).
(23) (a) M. M. Warshaw and I. Tinoco, Jr., *J. Mol. Biol.*, **13**, 54 (1965); (b) *ibid.*, **20**, 29 (1966).

or stacked conformations. Since the magnitude of the hypochromism is dependent upon the thermodynamic strength of the interaction[24] and upon the relative orientation of the transition moments,[14,15] it is instructive to examine the latter dependence with respect to the four compounds **1**, **4**, **12**, and **19**. It is recognized that the trimethylene linkage between two N^6 positions may not be equivalent to linkage between any two ring positions since, in the former case, five linking atoms are involved. However, it is logical to assume that the most stable conformations of **4** will be those favoring orbital overlap of the N electrons with the π cloud of the purine ring system, and hence that the separation between the two rings will not be of greater effective length than a three-atom bridge. For the N^6,9′-trimethylenebisadenine isomer (**12**), even though the $-(CH_2)_3NH-$ group may similarly be considered to be effectively a three-atom bridge, in this model the two adenine rings are shifted laterally and cannot overlap as completely as in the other isomers. The isomer Ade^6-C_3-Ade^9 (**12**) comes closest to being capable of assuming a folded conformation with the adenine rings in similar relation to that calculated by Pullman and Pullman[25] (Ade^7-C_3-Ade^8 could also assume such a conformation but has not been made) to be the most probable arrangement for the stacking of two purines (adenines) at interplanar distance 3.4 Å. Yet this isomer does not show the greatest hypochromism among the six investigated. There is little difference between the hypochromisms exhibited by Ade^9-C_3-Ade^9 (**1**) and Ade^6-C_3-Ade^6 (**4**), and in both isomers the trimethylene bridge permits (but does not dictate) the same type of overlap between the adenine rings in folded conformations, whether in "straight stack" or "alternate stack," as defined by Broom, Schweizer, and Ts'o[26] and related to self-association. We have thus far refrained from committing ourselves as to the conformational populations of Ade^9-C_3-Ade^9 (**1**)[6] and Ade^6-C_3-Ade^6 (**4**) in dilute solution pending the accumulation of further data.[13] Compound **19**, Ade^7-C_3-Ade^9, the fourth isomer with % hypochromism in the same range (along with **1**, **4**, and **12**) can assume two families of conformations oscillating about those in which the 4–5, 5–4 bonds are either parallel (*i.e.*, the overlapping adenines are facing in opposite directions) or orthogonal. A comparison of the ultraviolet absorption curves for **19** and **1**, in relation to those of their component propyladenine half-molecules, indicates a greater diminution in the B_{1u} transition in the former and in the B_{2u} transition[27-31] in the latter.

The other striking feature in the per cent hypochromisms listed in Table I lies in the high H values calculated for Ade^8-C_3-Ade^8 (**7**) and Ade^8-C_3-Ade^9 (**15**), 21.2 and 19.2, respectively, which are significantly above the H range for the other four isomers (the former despite the hyperchromic effect above 280 nm).[13] What, then, is different about folded or stacked conformations available to compounds **7** and **15**? The 8,8′ isomer is pivotal in that the adenine rings can be stacked facing in the same direction or in the opposite direction. It seems unlikely that in the most stable folded conformation they would be facing in the same direction, since then the intramolecular interaction, as measured by H, would be expected to lie in the same range for compounds **1** and **4**, whereas **7** is clearly out of line (H = 21.2). Folded conformations of **7** with the adenine rings facing opposite would thus appear to be favored. One of the minimum-energy possibilities is **20**, in which each adenine NH_2 group



20



21

can lie over the six-membered ring of the other adenine moiety. This type of conformation is very similar to that concluded for adenylyl(5′–5′)adenosine($A_{5'}$-$p_{5'}$A) by Kondo, Holmes, Stempel, and Ts'o[32] from their study of the interaction of two adenines in dinucleoside monophosphates joined at different positions by a phosphodiester linkage (2′–5′, 3′–5′, and 5′–5′). Their conclusions were reached using three physicochemical methods, namely, proton magnetic resonance, circular dichroism, and ultraviolet absorbance. A comparison of the extinction coefficients at λ_{max} for $A_{5'}p_{5'}A$ *vs.* AMP showed a hypochromicity of 22%, which was maximal for their series and much higher than the hypochromicities observed for the isomers $A_{3'}p_{5'}A$ (12%) and $A_{2'}p_{5'}A$ (16%).[32] For the trimethylene-bridged compounds 8,8′-trimethylenebistheophylline[8] and 1,1′-trimethylenebisthymine[7] in the crystal, X-rays show the opposite facings of the rings making up each molecule. While Thy-C_3-Thy assumes C_2 crystallographic symmetry,[7] however, the rings must be able to face in the same direction ("straight" or "parallel stack") in aqueous solution in order to account for the *cis-syn*-cyclobutane geometry (C_s symmetry) of its photoproduct in that solvent.[3]

In the case of the 8,9′ isomer with H = 19.2, it is possible for only one adenine NH_2 group to lie over the pyrimidine ring of the other adenine in a folded conformation (**21**). These conformations (**20** and **21**) suggest negative enthalpy to be derived from n–π in addition to π–π overlap and are consistent with the X-ray findings that, in the crystal, base overlap is usually accomplished by positioning polar substituents, including the NH_2 group, over the ring system of an adjacent base.[33] Both Ade^8-C_3-Ade^8 (**7**) and Ade^8-C_3-Ade^9 (**15**) (Ade^7-C_3-Ade^9 (**19**) cannot readily assume NH_2/pyrimidine ring overlapping conformations) can approximate the "alternate stack" conformation de-

(24) D. Poland, J. N. Vournakis, and H. A. Scheraga, *Biopolymers*, **4**, 223 (1966).
(25) B. Pullman and A. Pullman, *Progr. Nucl. Acid Res. Mol. Biol.*, **9**, 327 (1969); see especially p 371.
(26) A. D. Broom, M. P. Schweizer, and P. O. P. Ts'o, *J. Amer. Chem. Soc.*, **89**, 3612 (1967).
(27) L. B. Clark and I. Tinoco, *ibid.*, **87**, 11 (1965).
(28) (a) R. F. Stewart and N. Davidson, *J. Chem. Phys.*, **39**, 255 (1963); (b) E. Charney and M. Gellert, *Biopolym., Symp.*, 1, 469 (1964); (c) R. F. Stewart and L. H. Jensen, *J. Chem. Phys.*, **40**, 2071 (1964).
(29) W. Voelter, G. Barth, R. Records, E. Bunnenberg, and C. Djerassi, *J. Amer. Chem. Soc.*, **91**, 6165 (1969).
(30) W. Voelter, R. Records, E. Bunnenberg, and C. Djerassi, *ibid.*, **90**, 6163 (1968).
(31) D. W. Miles, M. J. Robins, R. K. Robins, and H. Eyring, *Proc. Nat. Acad. Sci. U. S.*, **62**, 22 (1969).
(32) N. S. Kondo, H. M. Holmes, L. M. Stempel, and P. O. P. Ts'o, *Biochemistry*, **9**, 3479 (1970). We are grateful to Professor Ts'o for helpful discussion concerning these conformations.
(33) C. E. Bugg, J. M. Thomas, M. Sundaralingam, and S. T. Rao, *Biopolymers*, **10**, 175 (1971).

Table II. Quantitative Electronic Absorption Data in Water

Compd	No.	Neutral				0.1 N HCl				0.1 N NaOH			
		λ_{max}	ϵ	λ_{min}	ϵ	λ_{max}	ϵ	λ_{min}	ϵ	λ_{max}	ϵ	λ_{min}	ϵ
Ade^{9}-C_3	2	261	14,390	228	2400	259	14,180	231	3060	261.5	14,360	228	2310
Ade^{7}-C_3		272	10,290	231.5	3330	272.5	13,630	237	3690	271.5	10,320	231.5	3460
		267.5	10,250							268.5	10,290		
		280 sh[a]	6,570							280 sh[a]	6,650		
Ade^{8}-C_3		262.5	15,240	227.5	3150	266.5	15,140	231	2880	270	14,530	239	3870
Ade^{6}-C_3		268	17,300	229	2020	270	16,000	233	2580	274.5	15,820	239.5	3380
										281 sh[a]	13,500		
Ade^{9}-C_3-NH_2	11	261	14,390	227.5	2320	258.5	14,040	229	2950	261	14,470	228	2640
Ade^{6}-C_3-$^{+}NH_3Cl^{-}$		267	17,300	229	2260	273	16,440	233.5	2590	274	17,210	240.5	3470
										281.5 sh[a]	13,350		
Ade^{8}-C_3-Ade^{8}	7	260	21,590	232	7040	264.5	25,540	232	6000	271	28,920	239.5	7440
Ade^{6}-C_3-Ade^{9}	12	260	25,180	230	5480	262	25,990	232.5	6570	263.5	23,570	237	7660
										271 sh[a]	20,150		
										279.5 sh[a]	13,220		
Ade^{7}-C_3-Ade^{9}	19	265	17,230	233	7010	266	21,390	235	7500	265.5	17,270	232.5	7000
Ade^{8}-C_3-Ade^{9}	15	259	21,690	230	6020	261	24,690	231.5	6800	264	21,990	237.5	8120
Ade^{6}-C_3-Ade^{6}	4	262.5	27,000	230	4950	272	27,810	233.5	5320	274.5	32,340	240.5	6540
										282 sh[a]	27,310		

[a] Abbreviation sh = shoulder.

fined by Broom, *et al.*[26] In any case, the two isomers **7** and **15** are unique in exhibiting greater hypochromism than the other isomers. Since the aqueous solutions used for the electronic spectral determinations are sufficiently dilute, we can be sure that only intramolecular interactions are being observed, but the percentages of hypochromism provide mainly suggestions as to the degree and orientation of intramolecular stacking. Taken in conjunction with molecular models of the various trimethylenebisadenines here studied, in which the positions of bridge attachment to the adenine rings control or delimit the ring-overlapping conformations, the possibilities can be further refined. For more definite conclusions concerning orientation within the stacked conformations, it has been necessary to turn to magnetic circular dichroism studies,[13] which will be discussed in a sequel.

Experimental Section[34]

Electronic Absorption Spectra. The quantitative ultraviolet spectrometric measurements of the trimethylenebisadenines and the corresponding propyladenines were made with a Cary Model 15 spectrophotometer as described previously,[6] using neutral, aqueous solution ($3-8 \times 10^{-5}$ *M*). The spectra were determined three times and average values were used. Oscillator strength and hypochromism values were calculated as described previously.[6] The spectra of these compounds were also determined in dilute HCl and NaOH solutions and those of the intermediates were determined only once. The quantitative data are listed in Table II.

Chromatography. Homogeneity of the trimethylenebisadenines and the corresponding propyladenines was established by tlc on silica gel (Eastman Chromagram sheets) in four different solvent systems: A, chloroform–acetic acid–methanol (7:2:1); B, formic acid–chloroform (1:4); C, methanol–acetic acid (7:3); D, ethanol–chloroform–formic acid (5:4:1).

Synthesis. The following compounds had been prepared before: 9-propyladenine (**2**),[6,20,35] 6-propylaminopurine,[6,36] and 9-(3-aminopropyl)adenine (**11**).[20]

6-(3-Aminopropylamino)purine hydrochloride[19b] was found to have mp 256–257° dec rather than 325° dec as reported;[19b] therefore, additional identifying data are provided: nmr (CF_3COOH) τ 0.32 (br s, 1, AdC_6NH), 0.98 and 1.12 (2s, 2, $AdC_{2,8}H$), 2.82 (br s, 3, $^{+}NH_3$), 5.85 (m, 2, $AdNHCH_2$), 6.45 (m, 2, CH_2N), 7.46 (m, 2, CCH_2C); mass spectrum (70 eV) *m/e* (rel intensity) 192 (13, M^{+} − HCl), 163 (12), 162 (92), 149 (100), 148 (50), 136 (23), 135 (40), 121 (24), 120 (34), 119 (31), 108 (22). The ultraviolet data recorded in Table II were determined in 0.05 *M* phosphate buffer.

Anal. Calcd for $C_8H_{13}ClN_8$: C, 42.01; H, 5.73; N, 36.74; Cl, 15.52. Found: C, 42.02; H, 5.72; N, 36.69; Cl, 15.53.

N^6,$N^{6'}$-Trimethylenebisadenine (4).[19] This compound was prepared by refluxing a mixture of 114 mg (1.5 mmol) of 1,3-diaminopropane, 303 mg (3 mmol) of triethylamine, and 464 mg (3 mmol) of 6-chloropurine in 10 ml of 1-butanol for 2.5 hr and recrystallizing the product from acetic acid–ethanol (1:1, v/v) to yield 87% of product. Analytically pure material was obtained by dissolution in hot concentrated aqueous ammonia, partial evaporation, and precipitation when cold: mp >320°; nmr (CF_3COOH) τ 0.39 (br s, 2, AdC_6NH), 1.00 and 1.17 (2s, 4, $AdC_{2,8}H$), 5.87 (m, 4, NCH_2C), 7.52 (m, 2, CCH_2C); mass spectrum (70 eV) *m/e* (rel intensity) 310 (2, M^{+}), 309 (8), 175 (21), 163 (10), 162 (100), 149 (73), 148 (25), 135 (20), 121 (18), 120 (26), 119 (25), 108 (10).

Anal. Calcd for $C_{13}H_{14}N_{10}$: C, 50.31; H, 4.55; N, 45.14. Found: C, 50.19; H, 4.66; N, 44.86.

The bispicrate was made (in acetic acid) for comparison with this derivative previously described and was recrystallized from aqueous solution as yellow needles, mp 282–283° dec (lit.[19b] 274–275° dec).

4-(Aden-8-yl)butyric acid (6) was prepared by the Traube method.[37] A mixture of 1.25 g (10 mmol) of 4,5,6-triaminopyrimidine (**5**) and 6.6 g (50 mmol) of glutaric acid was heated at 175–180° in an oil bath under a slow stream of nitrogen while the mixture gradually melted. A small amount of water was distilled first and finally glutaric acid was sublimed. After the reaction mixture was stirred and heated at 175–180° for 3 hr, it was cooled and the solid was triturated and washed with ethanol to remove excess glutaric acid. The solid was recrystallized from dry dimethylformamide to yield 1.0 g (45%) of the desired product, homogeneous on tlc (silica gel). Further recrystallization from anhydrous dimethylformamide yielded an analytically pure sample as prisms: mp 294–296° dec; $\lambda_{max}^{H_2O}$ 262.5 nm (ϵ 14,200), $\lambda_{min}^{H_2O}$ 229 (3150), $\lambda_{max}^{0.1N\ HCl}$ 266.5 (14,180), $\lambda_{min}^{0.1N\ HCl}$ 231 (2750), $\lambda_{max}^{0.1N\ NaOH}$ 270.5 (13,590), $\lambda_{min}^{0.1N\ NaOH}$ 239.5 (4730); nmr (CF_3COOH) τ *ca.* 0.80 (br s, 2, AdC_6NH_2), 1.22 (s, 1, AdC_2H), 6.60 (t, J = 6.5 Hz, 2, AdC_8CH_2), 7.09–7.69 (m, 4, CCH_2CH_2CO).

Anal. Calcd for $C_9H_{11}N_5O_2$: C, 48.87; H, 5.01; N, 31.66. Found: C, 48.68; H, 5.20; N, 31.18.

8,8′-Trimethylenebisadenine (7). An 884-mg (4 mmol) portion

(34) All melting points are corrected. Nuclear magnetic resonance spectra were determined on a Varian Associates A-60A spectrometer using tetramethylsilane as internal standard. Electronic absorption spectra were recorded on a Cary Model 15 spectrophotometer. Microanalyses were performed by Mr. J. Nemeth and his staff, who also weighed samples for quantitative electronic absorption studies. Mass spectra were determined by Mr. J. Wrona using a Varian-MAT Model CH-5 low-resolution spectrometer.

(35) C. Temple, Jr., C. L. Kussner, and J. A. Montgomery, *J. Med. Pharm. Bull.*, **5**, 866 (1962).

(36) C. G. Skinner, W. Shive, R. G. Ham, D. C. Fitzgerald, Jr., and R. E. Eakin, *J. Amer. Chem. Soc.*, **78**, 5097 (1956).

(37) *E.g.*, see A. Giner-Sorolla and A. Bendich, *ibid.*, **80**, 5744 (1958).

of powdered 4-(aden-8-yl)butyric acid (**6**) and 600 mg (4.8 mmol) of powdered 4,5,6-triaminopyrimidine (**5**) were mixed well and heated at 250–260° (metal bath temperature) for 4 hr while partial melting was observed. Unreacted 4,5,6-triaminopyrimidine sublimed at the end of the reaction and was discarded. After cooling, the brown reaction product was recrystallized once from acetic acid with the addition of activated charcoal, yielding 1.2 g of pale-brown powder which was dissolved in a minimum amount of formic acid. The formic acid solution was applied to a column (100 g) of silica gel packed with chloroform–acetic acid–methanol (85:10:5, v/v). The desired product was eluted with the same solvent system. A middle fraction was dissolved in hot concentrated ammonia, activated charcoal was added, and the mixture was filtered. The filtrate, after the slow evaporation to remove most of the ammonia, was cooled, yielding 480 mg (39%) of analytically pure material as prisms. Drying for 5 hr *in vacuo* at refluxing xylene temperature afforded an anhydrous sample: mp >320°; nmr (CF_3COOH) τ 0.92 (v br s, 4, AdC_6NH_2), 1.23 (s, 2, AdC_2H), 6.36 (t, J = 7 Hz, 4, AdC_8CH_2), 7.13 (m, 2, CCH_2C); mass spectrum (70 eV) *m/e* (rel intensity) 310 (2, M^+), 163 (10), 162 (100), 149 (72).

Anal. Calcd for $C_{13}H_{14}N_{10}$: C, 50.31; H, 4.55; N, 45.14. Found: C, 50.09; H, 4.55; N, 45.06.

N^6,9′-Trimethylenebisadenine (12). A mixture of 577 mg (3 mmol) of 9-(3-aminopropyl)adenine (**11**)[20] and 232 mg (1.5 mmol) of 6-chloropurine (**3**) in 10 ml of 1-butanol was stirred vigorously at reflux for 5 hr. The reaction mixture was concentrated to dryness under reduced pressure, and the residue was washed several times with water, leaving 377 mg (81%) of the desired product, homogeneous on tlc (silica gel). Recrystallization of a small portion of the product from acetic acid–ethanol (1:1, v/v) afforded a powder, mp >320°, which was shown by nmr to be the acetate salt. Another portion of the product was dissolved in hot concentrated ammonia and filtered, and the filtrate was evaporated slowly to remove most of the ammonia. The solution was cooled overnight, depositing analytically pure monohydrate as hygroscopic prisms, mp >320°.

Anal. Calcd for $C_{13}H_{16}N_{10}O$: C, 47.54; H, 4.91; N, 42.67. Found: C, 47.93; H, 4.98; N, 42.99.

Drying for 15 hr *in vacuo* at refluxing xylene temperature gave the anhydrous base: mp >320°; nmr (CF_3COOH) τ 0.33 (br s, 3, AdC_6NH_2 and AdC_6NH), 0.72, 1.02, 1.15, and 1.30 (4 s, 4, $AdC_{2,8}H$), 5.17 (t, J = 7 Hz, 2 $AdCH_2$), 5.85 (m, 2, CCH_2N), 7.32 (m, 2, CCH_2C); mass spectrum (70 eV) *m/e* (rel intensity) 310 (5, M^+), 175 (63), 174 (12), 163 (12), 162 (100), 149 (48), 148 (64), 136 (24), 135 (22), 119 (18), 108 (12).

Anal. Calcd for $C_{13}H_{14}N_{10}$: C, 50.31; H, 4.55; N, 45.14. Found: C, 50.25; H, 4.59; N, 45.29.

Ethyl 4-(Aden-9-yl)butyrate (13). An 8.0-g (33 mmol) portion of ethyl 4-iodobutyrate, bp 101–103° (13 nm), freshly prepared[38] from ethyl 4-chlorobutyrate, in 20 ml of dry dimethylformamide was added slowly under nitrogen to the vigorously stirred suspension of 30 mmol of sodium adenide in 180 ml of dry dimethylformamide, and stirring was continued under nitrogen at ambient temperature for 2 days while the mixture became gradually homogeneous. The solvent was removed under reduced pressure and the residue was triturated with dry ether to yield a white powder which was filtered and added to a large amount of chloroform (*ca.* 700 ml). The chloroform suspension was filtered to remove sodium iodide, and the filtrate was concentrated again to dryness under reduced pressure, leaving 6.1 g of crude product. Recrystallization from 1-butanol yielded 3.7 g (49%) of analytically pure material as long prisms: mp 108–109°; $\lambda_{max}^{H_2O}$ 261.5 nm (ϵ 14,160), $\lambda_{min}^{H_2O}$ 227.5 (2390), $\lambda_{max}^{0.1N\ HCl}$ 258.5 (12,960), $\lambda_{min}^{0.1N\ HCl}$ 230 (2820), $\lambda_{max}^{0.1N\ NaOH}$ 261 (14,430), $\lambda_{min}^{0.1N\ NaOH}$ 228.5 (2420); nmr ($CDCl_3$) τ 1.67 and 2.19 (2 s, 2, $AdC_{2,8}H$), 3.43 (br s, 2, AdC_6NH_2), 5.71 (t, 2, J = 7 Hz, $AdCH_2$), 5.88 (q, 2, J = 7 Hz, $COOCH_2$), 7.53–7.97 (m, 4, CCH_2CH_2CO), 8.76 (t, 3, J = 7 Hz, CH_3).

Anal. Calcd for $C_{11}H_{15}N_5O_2$: C, 53.00; H, 6.21; N, 28.09. Found: C, 52.71; H, 5.98; N, 28.23.

4-(Aden-9-yl)butyric Acid (14).[39] A 1.6-g portion of ethyl 4-(aden-9-yl)butyrate in 15 ml of 1 *N* NaOH was allowed to stand for 20 hr and then made slightly acidic by addition of aqueous acetic acid in the cold. The resulting precipitate was collected, washed, and dried, affording 1.4 g (quantitative) of almost pure product. A small portion was recrystallized from dry dimethylformamide to afford prisms: mp 296–297° dec; $\lambda_{max}^{H_2O}$ 261.5 nm (ϵ 13,950), $\lambda_{min}^{H_2O}$ 228.5 (2560), $\lambda_{max}^{0.1N\ HCl}$ 258.5 (13,650), $\lambda_{min}^{0.1N\ HCl}$ 230 (2820), $\lambda_{max}^{0.1N\ NaOH}$ 261 (14,050), $\lambda_{min}^{0.1N\ NaOH}$ 228 (2430); nmr (CF_3COOH) τ 0.77 and 1.25 (2 s, 2, $AdC_{2,8}H$), 5.20 (t, 2, J = 6.5 Hz, $AdCH_2$), 7.13–7.59 (m, 4, CCH_2CH_2CO).

Anal. Calcd for $C_9H_{11}N_5O$: C, 48.87; H. 5.08; N, 31.66. Found: C, 48.87; H, 4.97; N, 31.48.

8,9′-Trimethylenebisadenine (15). An 884-mg (4 mmol) portion of powdered 4-(aden-9-yl)butyric acid (**14**) and 600 mg (4.8 mmol) of powdered 4,5,6-triaminopyrimidine (**5**) were mixed well and heated at 250–260° (metal bath temperature) for 1 hr while the mixture melted, foamed, and finally solidified. Most of the unreacted 4,5,6-triaminopyrimidine was sublimed at the end of the reaction and discarded. After cooling, the reaction mixture was dissolved in aqueous acetic acid, treated with activated charcoal, and filtered. The filtrate was made slightly alkaline in the cold with aqueous ammonia, and the resulting precipitate was filtered and dried, affording 900 mg of pale-green powder. This crude product was dissolved in a minimum amount of formic acid, and the solution was applied to a column containing 100 g of silica gel packed with chloroform–acetic acid–methanol (85:10:5, v/v). The desired product was eluted slowly with the same solvent system. A middle fraction (450 mg) was dissolved in hot concentrated ammonia, treated with activated charcoal, and filtered. The filtrate, after slow evaporation to remove most of the ammonia, was cooled, yielding 240 mg (20%) of analytically pure material as prisms. Drying for 10 hr at refluxing xylene temperature afforded an anhydrous sample: mp >320°; nmr (CF_3COOH) τ 0.84, 1.28, and 1.31 (3 s, superimposed on a br resonance, 7, $AdC_{2,8}H$ and AdC_8NH_2), 5.18 (t, J = 6.5 Hz, 2, $AdCH_2$), 6.46 (t, J = 6.5 Hz, 2, AdC_8CH_2), 7.18 (m, 2, CCH_2C); mass spectrum (70 eV) *m/e* (rel intensity) 310 (6, M^+), 175 (33), 162 (100), 149 (19), 148 (26), 145 (12).

Anal. Calcd for $C_{13}H_{14}N_{10}$: C, 50.31; H, 4.55; N, 45.14. Found: C, 50.00; H, 4.59; N, 44.94.

5-*N*-(3-Bromopropyl)formylamino-4,6-diaminopyrimidine (17). To a suspension of 1.38 g (9 mmol) of 4,6-diamino-5-formylaminopyrimidine (**16**) in 50 ml of dry dimethylformamide stirred under nitrogen was added 0.24 g (10 mmol) of pentane-washed sodium hydride.[21] The mixture was stirred vigorously at ambient temperature for 2 hr, and the resulting homogeneous solution was then transferred under nitrogen to a pressure equalizing dropping funnel. The solution was added slowly to a vigorously stirred solution of 18.2 g (90 mmol) of 1,3-dibromopropane in 10 ml of dry dimethylformamide. After additional stirring under nitrogen for 2.5 hr at ambient temperature, the solution, which showed two new spots on tlc (silica gel), was poured into 500 ml of ether with stirring and the mixture was allowed to stand overnight. The precipitate was filtered and washed with water, methanol, and then with ether. The crude product, homogeneous on tlc (silica gel), was recrystallized from *ca.* 100 ml of 1-butanol and dried, yielding 1.4 g (57%) of prisms: mp *ca.* 170°, dec at 185°; nmr (CF_3COOH) τ 1.52 (s, 2, PyC_2H and CHO), 2.70 (br s, 4, NH_2), 6.03 (t, J = 7 Hz, 2, NCH_2C), 6.55 (t, J = 7 Hz, 2, CCH_2Br), 7.50–7.93 (m, 2, CCH_2C).

Anal. Calcd for $C_8H_{12}BrN_5O$: C, 35.15; H, 4.41; N, 25.55. Found: C, 35.87; H, 4.45; N, 26.02.

5-*N*-[3-(Aden-9-yl)propyl]formylamino-4,6-diaminopyrimidine (18). A 1.65-g portion (6 mmol) of 5-*N*-(3-bromopropyl)formylamino-4,6-diaminopyrimidine (**17**) was added to a stirred suspension of 6 mmol of sodium adenide in 60 ml of dry dimethylformamide. The resulting suspension was stirred vigorously and heated at 100° for 24 hr while the mixture became homogeneous at first and then gradually heterogeneous again. The solvent was removed from the reaction mixture under reduced pressure, and the residue was triturated with ether, filtered, and washed well with water to remove sodium bromide. After drying, the crude product was dissolved in aqueous acetic acid, treated with activated charcoal, and filtered. To the cold filtrate was added aqueous ammonia until precipitation had begun in slightly alkaline medium. The cold suspension was filtered and dried, yielding 1.3 g (66%) of white amorphous powder, homogeneous on tlc (silica gel), mp >300°, which was used for the next step without further purification: nmr (CF_3COOH) τ 0.85 (br s, 2, AdC_6NH_2), 1.32, 1.40, 1.50, and 1.67 (4 s, 4, PyC_2H, CHO, and $AdC_{2,8}H$), 2.67 (br s, 4, NH_2), 5.25 (unresolved signal, 2, $AdCH_2$), 6.00 (unresolved signal, 2, NCH_2C), 7.42 (unresolved signal, 2, CCH_2C).

Anal. Calcd for $C_{13}H_{16}N_{10}O$: C, 47.54; H, 4.91; N, 42.67. Found: C, 48.44; H, 4.91; N, 42.50.

7,9′-Trimethylenebisadenine (19). A mixture of 985 mg (3 mmol) of 5-*N*-[3-(aden-9-yl)propyl]formylamino-4,6-diaminopyrimidine

(38) N. J. Leonard, R. C. Fox, and M. Oki, *J. Amer. Chem. Soc.*, 76, 5711 (1954).

(39) D. H. De Kock and H. G. Raubenheimer, *J. S. Afr. Chem. Inst.*, 24, 91 (1971).

(18) and 100 mg of anhydrous potassium carbonate in 50 ml of dry dimethylformamide was stirred and heated at reflux for 6 hr. The solvent was removed under reduced pressure, and the residue, which was washed well with water and dried, was recrystallized from acetic acid–methanol (1:1, v/v) yielding 600 mg of powder. This crude product was dissolved in a minimum amount of formic acid, and the solution was applied to a column (100 g) of silica gel packed in chloroform–acetic acid–methanol (7:2:1, v/v). Elution with the same solvent mixture yielded the desired product. A middle fraction was dissolved in hot aqueous acetic acid, treated with activated charcoal, and filtered. Cold aqueous ammonia was added to the filtrate until precipitation was complete in the slightly basic medium. The cold suspension was filtered to yield 365 mg (39%) of analytically pure material as prisms. Drying for 10 hr *in vacuo* at refluxing xylene temperature afforded an anhydrous sample: mp >320°; nmr (CF_3COOH) τ 0.83, 0.90, 1.15, and 1.30 (4 s superimposed on a br resonance, 8, $AdC_{2,8}H$ and AdC_6NH_2) 5.03 (m, 4, $AdCH_2$ and AdN_7CH_2), 7.05 (m, 2, CCH_2C); mass spectrum (70 eV) *m/e* (rel intensity) 310 (1, M^+), 176 (25), 175 (95), 174 (19), 162 (100), 149 (22), 148 (74), 136 (15), 135 (19), 108 (14).

Anal. Calcd for $C_{13}H_{14}N_{10}$: C, 50.31; H, 4.55; N, 45.14. Found: C, 50.14; H, 4.69; N, 45.20, 44.98.

8-Propyladenine was made from 4,5,6-triaminopyrimidine (**5**) and *n*-butyric acid by the general method.[37] Sublimation of the product yielded leaflets: yield 68%; mp 261–262°; nmr (CF_3COOH) τ 1.22 (s, 1, AdC_2H), 6.64 (t, 2, J = 7 Hz, AdC_8CH_2), 7.92 (m, 2, J = 7 Hz, CCH_2C), 8.81 (t, 3, J = 7 Hz, CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 177 (26, M^+), 162 (19), 149 (100), 148 (26), 121 (25).

Anal. Calcd for $C_8H_{11}N_5$: C, 54.22; H, 6.26; N, 39.52. Found: C, 54.51; N, 6.15; N, 39.68.

4,6-Diamino-5-*N*-propylformylaminopyrimidine (17, Br = H). This intermediate was made by the general method previously described,[21] yield 77%, small prisms from 1-butanol: mp 291–292°; nmr (CF_3COOH) τ 1.53 (s, 2, PyC_2H and CHO), 3.80 (br s, 4, NH_2), 6.60 (t, J = 7 Hz, 2, NCH_2C), 7.88–8.50 (m, 2, CCH_2C), 8.97 (t, J = 7 Hz, 3, CH_3).

Anal. Calcd for $C_8H_{13}N_5O$: C, 49.23; H, 6.71; N, 35.88. Found: C, 48.96; H, 6.59; N, 36.04.

7-Propyladenine. The intermediate described above was cyclized in the usual manner[21] to give 7-propyladenine, yield 57%, prisms from 2-propanol: mp 204–205°; nmr (CF_3COOH) τ 0.83 and 1.13 (2s, 2, $AdC_{2,8}H$), 5.23 (t, 2, J = 7 Hz, AdN_7CH_2), 7.80 (m, 2, J = 7 Hz, CCH_2C), 8,86 (t, 3, J = 7 Hz, CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 177 (100, M^+), 162 (17), 148 (37), 135 (76), 121 (29), 108 (24), 94 (26).

Anal. Calcd for $C_8H_{11}N_5$: C, 54.22; H, 6.26; N, 39.52. Found: C, 54.13; H, 6.28; N, 39.34.

Reactions of 2-Acyloxyisobutyryl Halides with Nucleosides. I.[1] Reactions of Model Diols and of Uridine

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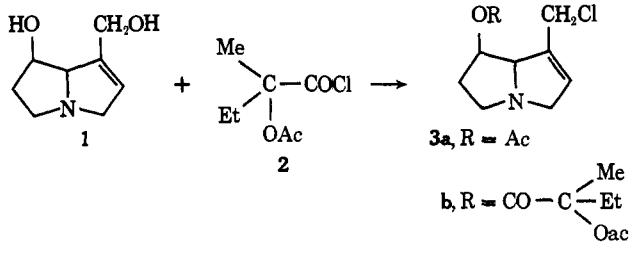
Contribution No. 98 from the Institute of Molecular Biology, Syntex Research, Palo Alto, California. Received November 18, 1972

Abstract: The reaction of 2-acetoxyisobutyryl chloride with hydroxyl groups and with vicinal diols has been examined in detail. Isolated hydroxyl groups are usually converted into 2,5,5-trimethyl-1,3-dioxolan-4-on-2-yl ethers or, under certain conditions, 2-acetoxyisobutyryl esters. *cis*-Cycloalkane-1,2-diols are converted almost quantitatively into *trans*-2-chlorocycloalkyl acetates while the corresponding *trans*-1,2-diols give many products with little incorporation of chlorine. A mechanism is proposed for these reactions. The reaction of **4** with uridine, or with 5′-protected uridine derivatives, led to the formation in high yield of 3′-*O*-acetyl-2′-chloro-2′-deoxyuridines by way of a 2′,3′-acetoxonium ion and then a 3′-*O*-acetyl-O^2,2′-cyclonucleoside. The reaction with uridine has been studied in a number of solvents, the nature of the resulting 5′ substituent being solvent dependent. Evidence in support of the proposed mechanism is provided by the isolation or trapping of the intermediates from short reactions.

During studies by Mattocks on the chemistry of pyrrolizidine alkaloids, an abnormal reaction was observed between the 1,4-diol (**1**) and 2-acetoxy-2-methylbutyryl chloride (**2**), the unexpected products of this reaction being the chloroesters (**3a** and **3b**) in



yields of 54 and 20%.[3] Mattocks also showed that the acetoxyacyl chloride **2** reacts abnormally with 1,2- and 1,3-diols to form chloroacetates, for example, ethylene glycol reacting to form chloroethyl acetate. It was also reported that predominantly *trans*-cyclohexane-1,2-diol reacted to give four products, the major one of which was identified by vapor phase chromatography as *cis*-2-chlorocyclohexyl acetate, the reaction thus proceeding with inversion of one center.[4] On the basis of these, and other, considerations it was suggested that nucleophilic attack upon α-acyloxy acid chlorides bearing bulky substituents on the α positions occurred primarily at the acetoxy carbonyl group rather than at the acyl chloride function. A favored mechanism for these reactions is represented in eq 1.[3]

Our own interest in possible selective transformations of the vicinal diol grouping in ribonucleosides led us to reexamine this unusual reaction, and in the present paper we will discuss our interpretation of the

(1) For related work on halosugar nucleosides, see J. P. H. Verheyden and J. G. Moffatt, *J. Org. Chem.*, 37, 2289 (1972).
(2) Syntex Postdoctoral Fellow, 1965–1967.
(3) A. R. Mattocks, *J. Chem. Soc.*, 1918, 4840 (1964).
(4) This conclusion is somewhat confused by the fact that in the Experimental Section of his paper, Mattocks identifies the major product as the *trans*-chloroacetate while in the text it is referred to as the cis isomer.