stirring which was continued for 0.5 h. The solvent and excess of $CF_3CO_2D(H)$ were removed in vacuo and the residue extracted with pentane, leaving, after evaporation of the pentane, a yellow oil, which was again treated with 3 mL of CF_3CO_2D as described above, furnishing 300 mg (1.35 mmol, yield 75%) of (2,3-dimethylbutadiene-*1,1,4,4-d*$_4$)iron tricarbonyl. It contained, according to mass spectroscopy, 70 ± 3% tetradeuterated, 30 ± 3% trideuterated, and less than 5% di- and undeuterated adducts as determined by measuring the respective M^+ peaks; it was shown by ^1H NMR spectroscopic integration with benzene as reference that the methylene groups contained 90 ± 3% D and the methyl groups less than 3% D.

(b) Decomplexation of (2,3-Dimethylbutadiene-*1,1,4,4-d*$_4$)iron Tricarbonyl. This was accomplished according to the method of Shvo and Hazum.[58] A mixture of 300 mg (1.35 mmol) of (2,3-dimethylbutadiene-*1,1,4,4-d*$_4$)iron tricarbonyl, as obtained above, and 1.0 g (13 mmol) of Me_3NO (dried according to the procedure described above) in 10 mL of benzene was stirred at 40 °C for 2 days. The reaction mixture was filtered, liberated from excess Me_3NO and Me_3N by extraction with water, and dried over Na_2SO_4. The IR spectrum showed the absence of carbonyl absorptions. Comparison of the ^1H NMR spectrum of a sample of the obtained benzene solution with that of a benzene solution of undeuterated 2,3-dimethylbutadiene showed the deuterium content of the methylene absorption to be larger than 90%.

(c) $Fe_2(CO)_9$-Promoted Addition of CCl_4 to 2,3-Dimethylbutadiene-*1,1,4,4-d*$_4$. The benzene solution of 2,3-dimethylbutadiene-*1,1,4,4-d*$_4$, obtained as described above, was added to 30 mL of CCl_4 followed by addition of 700 mg (2 mmol) of $Fe_2(CO)_9$, and the reaction mixture was stirred overnight. The workup procedure was identical with that described for complex **15** and yielded, after chromatography, 70 mg (yield 15%, based on the intake of (2,3-dimethylbutadiene)iron tricarbonyl) of (D)-**15a**. It consists of 60 ± 3% **15**-d_4, 30 ± 3% **15**-d_3 and 10 ± 3% **15**-d_{0-2} as determined by the respective M^+ peaks and as checked by ^1H NMR spectroscopy. Structural assignment of (D)-**15a** is based on the following spectroscopic data: mass spectrum for $C_{10}H_5D_4{}^{35}Cl_3FeO_3$, *m/e* 342 ($M^+$), 314 ($M^+$ – CO), 286 (M^+ – 2 CO), 279 (M^+ – CO – ^{35}Cl), 268 (M^+ – 3 CO); IR (CCl_4) 2060, 1990, 1970 (CO) cm^{-1}; ^1H NMR, see Figure 2; ^{13}C NMR (C_6D_6) δ 211.1, 103.8, 99.2, 95.0, 43.6 (t, J_{CH} = 160 Hz), 21.0 (q, J_{CH} = 130 Hz). The signals observed at δ 58.4 (CH_2CCl_3) and 44.3 (=CH_2) for undeuterated **15** were of too low intensity to be observed in the case of (D)-**15** due to the lower spin response of deuterium in comparison with hydrogen.

Registry No. 1, 56745-77-8; 2, 50590-86-8; 3, 70130-71-1; 4, 70190-91-9; 5, 70130-73-3; 6, 70190-93-1; 7, 74397-50-5; 8, 74397-51-6; 9, 70130-72-2; 10, 70190-92-0; 11, 70130-76-6; 12, 70130-75-5; 13, 74397-52-7; 14, 74397-73-2; 15, 74397-74-3; (D)-15a, 74397-75-4; 16, 74397-76-5; 17, 60970-94-7; 18, 64314-99-4; 1-heptene, 592-76-7; 1,1,1,3-tetrachlorooctane, 18088-13-6; 1,5-hexadiene, 592-42-7; 5,7,7,7-tetrachloro-1-heptene, 51287-99-1; cyclohexene, 110-83-8; 2,3-dimethyl-2-butene, 563-79-1; 1-chloro-2-(trichloromethyl)cyclohexane, 7484-12-0; 1,1,1,3-trichloro-2,2,3-trimethylbutane, 74397-53-8; 4,4,4-trichloro-2,3,3-trimethyl-1-butene, 74397-54-9, 121-46-0; (*exo,exo*)-3-chloro-5-(trichloromethyl)tricyclo[2.2.1.0^{2,6}]heptane, 62991-86-0; (*endo,exo*)-3-chloro-5-(trichloromethyl)tricyclo-[2.2.1.0^{2,6}]heptane, 63039-08-7; 2,3-dimethylbutadiene, 513-81-5; 1,3-cyclohexadiene, 592-57-4; $Fe(CO)_5$, 13463-40-6; Me_3NO, 1184-78-7; $Me_3NFe(CO)_4$, 29863-43-2; $Fe(CO)_4Br_2$, 14878-20-7.

Utility of Purinyl Radicals in the Synthesis of Base-Modified Nucleosides and Alkylpurines: 6-Amino Group Replacement by H, Cl, Br, and I[1]

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When 9-substituted adenines are treated with *n*-pentyl nitrite in hydrogen atom donating solvents and the resulting reaction mixtures are warmed and photolyzed with visible light, the corresponding 9-substituted purines are isolated. The conversion apparently involves homolysis of the intermediate 6-diazonium salts or azo compounds to produce purinyl radical intermediates. These purinyl radicals can subsequently abstract hydrogen atoms from solvent molecules. We have utilized our deamination procedure for the direct synthesis of the antitumor antibiotic nebularine from adenosine. When the deaminations of 9-substituted adenines are conducted in dry CCl_4, $CHBr_3$, or CH_2I_2, the corresponding 6-chloro-, 6-bromo-, and 6-iodopurines are isolated in good yields. There appears to be no detectable hydrogen abstraction in competition with halogen abstraction in the cases of $CHBr_3$ and CH_2I_2 solvents. These transformations provide shortened preparative pathways to intermediates useful in the synthesis of other base-modified purines. Under appropriate reaction conditions, conversions to the 6–6′ dimers also may be possible. The type of transformation in this report represents one of the first examples of the use of neutral purinyl radicals in nucleic acid chemistry.

Modified nucleosides and nucleic acid bases have been extensively investigated due to their potential activity as antibiotics, enzyme inhibitors, and antitumor agents. For this reason, improved and abbreviated syntheses of such materials or their precursors are of considerable interest.

Recently we have communicated a new and direct synthesis for the adenosine deaminase inhibitor and nucleoside antibiotic nebularine (**1a**),[2,3] from readily available adenosine (**2a**), via the intermediacy of purinyl radicals.[4] These previously unreported purinyl radicals were generated in an anhydrous diazotization/deamination procedure using *n*-pentyl nitrite as the nitrosating agent. We now supply complete details for the synthesis of nebularine and 9-ethylpurine and extend the work to demonstrate the general utility of purinyl radical intermediates in the synthesis of 6-chloronebularine triacetate (**3b**), and its bromo and iodo congeners **4b** and **5b**, respectively, from triacetyladenosine (**2b**). From 9-ethyladenine (**6**), in addition to the deaminated compound **7**, 6-halo-9-ethyl-

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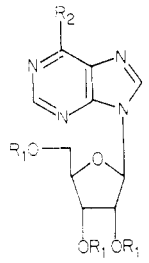
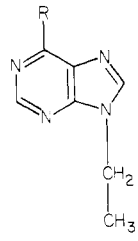
0022-3263/80/1945-3969$01.00/0

purines **8–10** have also been prepared.



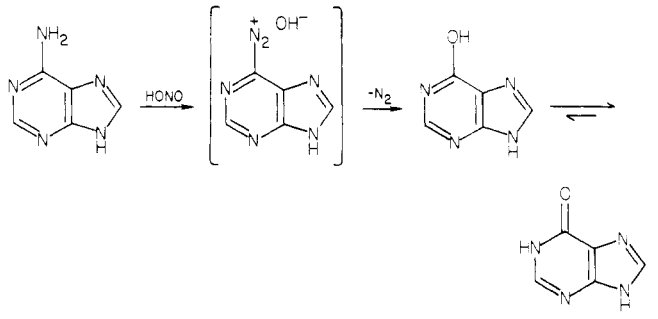


1a, R_1 = H; R_2 = H
1b, R_1 = $COCH_3$; R_2 = H
2a, R_1 = H; R_2 = NH_2
2b, R_1 = $COCH_3$; R_2 = NH_2
3a, R_1 = H; R_2 = Cl
3b, R_1 = $COCH_3$; R_2 = Cl
4a, R_1 = H; R_2 = Br
4b, R_1 = $COCH_3$; R_2 = Br
5a, R_1 = H; R_2 = I
5b, R_1 = $COCH_3$; R_2 = I

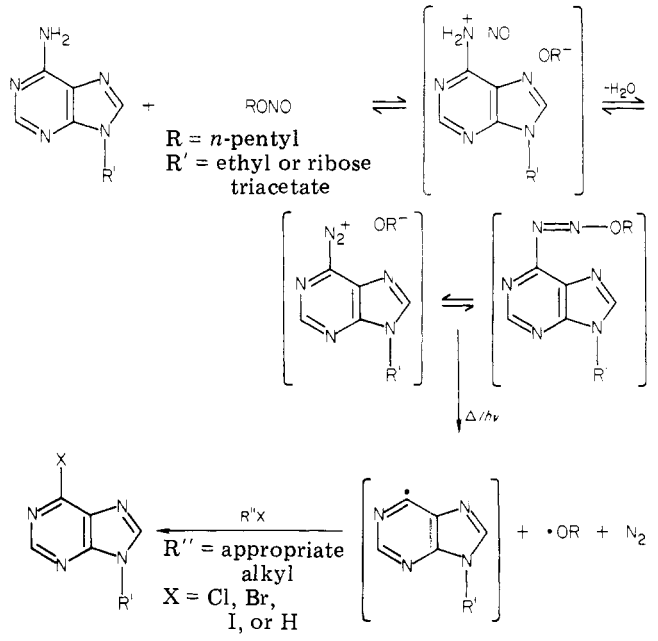
6, R = NH_2
7, R = H
8, R = Cl
9, R = Br
10, R = I

Older synthetic procedures for nebularine (**1a**) involved chloromercuripurinide fusion reactions with sugar derivatives such as chlorotriacetoribofuranose,[5] modified fusion reactions,[6] and longer syntheses involving catalytic hydrogenation of ring-halogenated materials[7] or of thioinosine.[8] Access to 9-alkylpurines from 9-alkyladenines or from other corresponding purines was previously limited. Such routes included alkylation of purine directly,[4] vinylation of purine followed by reduction,[9] reductive dehalogenation of appropriate halopurines,[10,11] or elaboration of 4,5-diaminopyrimidines.[11] Similarly, utilization of inconvenient starting materials or the use of comparatively severe reaction conditions was required for preparation of 6-chloro- and other 6-halo-9-alkylpurines or 6-halonucleosides. The halopurines are key intermediates in the synthesis of alkyl-,[12] aryl-,[12] thio-,[13] thioalkyl-,[14] azido-,[15] seleno-,[16] and most other C-6 substituted[17] purines. The chloro derivatives possess activity as chemotherapeutic agents[18] and are useful as biochemical probes for enzyme-catalyzed reactions.[19] Most chloropurines and the corresponding nucleosides were previously accessible only from hypoxanthine precursors through reaction with phosphorus halides, via sulfopurines by reaction with thionyl chloride, or from the corresponding chloropyrimidines.[20-22]

Scheme I



Scheme II



Results and Discussion

Although reductive deamination of aromatic amines with replacement by hydrogen of the amino group has been accomplished for many systems,[23] such diazotization/deamination reportedly fails under a variety of conditions for 6-aminopurine (adenine) derivatives.[15,24,25] While 6-diazonium salts of purine have not been isolated,[26] conversion of adenine to hypoxanthine in nitrous acid (Scheme I)[27] and of 6-aminopurine derivatives to the corresponding 6-fluoropurines[28,29] are presumptive of diazonium intermediates where the counterion acts as a nucleophile in an

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Table I. ^{13}C NMR Data for Substituted Purines

no.	compd	solvent	chemical shifts (δ) from Me_4Si C2	C4	C5	C6	C8	9-substituent carbons
1a	nebularine	D_2O	152.6	151.2	134.4	148.7	146.6	89.2, 86.4, 74.6, 71.2, 62.2
1b	2′,3′,5′-triacetylnebularine	$CDCl_3$	152.6	151.0	134.5	148.8	144.0	170.3, 169.6, 169.4, 86.5, 80.4, 73.0, 70.5, 63.0, 20.7, 20.5, 20.3
3b	2′,3′,5′-triacetyl-6-chloronebularine	$CDCl_3$	152.2	151.3	132.2	149.0	144.2	170.3, 169.6, 169.4, 86.9, 80.5, 73.1, 70.5, 63.0, 20.7, 20.5, 20.4
4b	2′,3′,5′-triacetyl-6-bromonebularine	$CDCl_3$	152.0	150.1	134.8	144.2	143.2	170.3, 169.6, 169.4, 86.9, 80.4, 73.1, 70.5, 63.0, 20.7, 20.5, 20.3
5b	2′,3′,5′-triacetyl-6-iodonebularine	$CDCl_3$	152.0	147.5	122.4	144.2	139.1	170.2, 169.6, 169.4, 86.9, 80.4, 73.0, 70.4, 62.9, 20.7, 20.5, 20.4
7	9-ethylpurine	$CDCl_3$	152.5	149.9	134.2	148.6	144.8	38.9, 15.3
8	6-chloro-9-ethylpurine	$CDCl_3$	151.9	151.0	131.7	149.2	144.7	39.6, 15.3
9	6-bromo-9-ethylpurine	$CDCl_3$	151.7	150.5	134.2	144.8	143.0	39.7, 15.3
10	6-iodo-9-ethylpurine	$CDCl_3$	151.8	148.0	122.1	144.2	138.7	39.6, 15.3

Table II. ^{1}H NMR Data for Substituted Purines

no.	compd	solvent	chemical shifts (δ) from Me_4Si H2	H6	H8	9-substituent protons
1a	nebularine	D_2O	8.63	8.97	8.81	6.1 (d), 4.1-4.9 (m), 3.85 (d)
1b	2′,3′,5′-triacetylnebularine	$CDCl_3$	8.40	9.18	9.01	6.33 (d), 6.03 (t), 5.73 (t), 4.45 (s), 2.17 (s), 2.11 (s), 2.09 (s)
3b	2′,3′,5′-triacetyl-6-chloronebularine	$CDCl_3$	8.53		8.79	6.33 (d), 6.01 (t), 5.71 (t), 4.46 (s), 2.18 (s), 2.12 (s), 2.11 (s)
4b	2′,3′,5′-triacetyl-6-bromonebularine	$CDCl_3$	8.51		8.74	6.35 (d), 6.01 (t), 5.70 (t), 4.47 (s), 2.17 (s), 2.12 (s), 2.10 (s)
5b	2′,3′,5′-triacetyl-6-iodonebularine	$CDCl_3$	8.46		8.79	6.29 (d), 5.98 (t), 5.67 (t), 4.45 (s), 2.17 (s), 2.12 (s), 2.10 (s)
7	9-ethylpurine	D_2O	8.29	8.77	8.63	4.25 (q), 1.45 (t)
8	6-chloro-9-ethylpurine	$CDCl_3$	8.17		8.76	4.38 (q), 1.60 (t)
9	6-bromo-9-ethylpurine	$CDCl_3$	8.30		8.70	4.43 (q), 1.63 (t)
10	6-iodo-9-ethylpurine	$CDCl_3$	8.24		8.63	4.39 (q), 1.61 (t)

ionic process. Interestingly, 8-diazonium salts of purines prepared from 8-amino substituted purines have been isolated and easily undergo many of the usual reactions of diazonium salts.[30]

We have discovered that 9-substituted 6-aminopurines when diazotized in an appropriate anhydrous medium under suitable reaction conditions are converted to the corresponding 9-substituted purines (Table IV). The procedure employs the known ability of alkyl nitrites to produce aryl radicals from arylamines and the subsequent ability of those radicals to react with suitable donor molecules.[31,32] The latter can be solvent. Among possible hydrogen atom donating solvents, dry tetrahydrofuran proved superior to dioxane, 2-propanol, cyclohexene, xylene, and various solvent mixtures. 1,1-Di-*o*-xylylethane solvent[33] also performed adequately as a hydrogen atom donor. Anhydrous carbon tetrachloride served satisfactorily as a chlorine atom donating solvent. Chloroform and methylene chloride were not employed due to their relatively low boiling points and the probability of competition between H abstraction and Cl abstraction by the purinyl radicals. The bond energy for C–H of 96–99 kcal/mol is close to the C–Cl bond energy of 79 kcal/mol.[35] Bromoform and diiodomethane proved to be satisfactory sources of bromine and iodine, respectively, for these 6-halopurine preparations (Scheme II). The energies of C–Br and C–I bonds, 66 and 52 kcal/mol,[35] respectively, are apparently sufficiently less than that of the C–H bond to avoid detectable competition of hydrogen with halogen abstraction. The apparent relative rates of reaction follow the order iodo > bromo > chloro for these three halomethanes.

In general, for adenine derivatives with appreciable solubility in the solvent, a solution containing a minimum of solvent was added dropwise to a warm, stirred mixture of solvent and dry distilled *n*-pentyl nitrite, under nitrogen in a vessel equipped with a bubbler. Sparingly soluble adenine derivatives were combined under nitrogen with solvent and *n*-pentyl nitrite at room temperature and warmed in the apparatus while the suspension was stirred. In all cases, constant illumination was supplied by a 200-W unfrosted tungsten lamp supported an inch from the reaction flask. Upon completion of the reaction (which may be monitored by gas chromatography or thin-layer chromatography of small aliquots), the solvent and unreacted pentyl nitrite were removed on a rotary evaporator. The resulting material was dissolved in 1:9 methanol–dichloromethane, dried (Na_2SO_4), and separated on silica gel

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Table III. Electronic Spectra for Substituted Purines

no.	compd	solvent	λ_{max}, nm	$\epsilon \times 10^{-3}$
1b	2',3',5'-triacetyl-nebularine	MeOH	262.0	7.5
3b	2',3',5'-triacetyl-6-chloronebularine	MeOH	263.5	9.7
4b	2',3',5'-triacetyl-6-bromonebularine	MeOH	266.2	9.3
5b	2',3',5'-triacetyl-6-iodonebularine	MeOH	273.5	10.4
7	9-ethylpurine	H_2O	264.5	8.0
8	6-chloro-9-ethyl-purine	H_2O	265.5	9.4
9	6-bromo-9-ethyl-purine	H_2O	267.5	9.0
10	6-iodo-9-ethyl-purine	H_2O	276.5	10.8

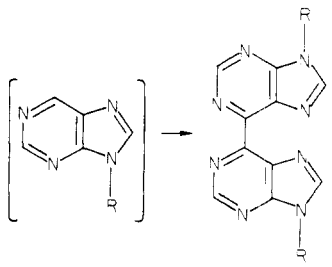
PF-254 plates. In the case of adenosine derivatives, the ribosyl hydroxyl groups were protected as the triacetate,[34] and this avoided possible formation of nitrite esters of the sugar in the subsequent diazotization reaction. The acetyl derivative gave enhancement of nucleoside solubility in organic solvents as well. After reaction, smooth convenient deprotection can be achieved by the methanolic ammonia method of Brown and Weliky.[5]

The structures of H-substituted products 1 and 7 were confirmed by ^{13}C, ^1H NMR, and UV spectrometric data comparison with authentic samples (see Tables I–III). Compound 7 was independently prepared from sodium purinide and ethyl tosylate in dimethylformamide.[36,37] Confirmation of the identities of the halogenated purines **3b**, **4b**, and **5b**, and 8–10 was obtained by ^{13}C and ^1H NMR spectroscopy and mass spectrometry (see Tables I–III).

9-Ethyl-6-chloropurine (8) obtained from our halogenation procedure was identical in all respects with authentic 8 prepared from 6-chloropurine and ethyl iodide in dimethyl sulfoxide.[10] Also, as radical processes are inhibited by the presence of scavengers such as O_2 and NO,[39] we found it desirable to purge the solvent with nitrogen and conduct the conversions under an atmosphere of nitrogen.

The mechanism of these transformations requires explanation. 6-Diazonium salts of purine may exist in equilibrium with the corresponding azo compounds (Scheme II). Both heat and certain frequencies of light are known to homolytically dissociate aryldiazonium salts and monoaryl azo compounds to yield aryl radicals.[40,41] The behavior of 6-diazonium salts and the corresponding azo compounds of purines may be analogous. Thus photolysis of our warmed reaction mixture would presumably result in the formation of purinyl radicals which could then abstract hydrogen atoms from tetrahydrofuran or halogen atoms from halocarbon solvents or undergo other radical reactions. Neutral purinyl radicals have not been reported previously although theoretical calculations on them have been undertaken.[38] Substantiating evidence for the intermediacy of purinyl radicals was provided by detection of hexachloroethane in the deamination reaction run in CCl_4. Hexachloroethane is the dimerization product of trichloromethyl radicals which are formed by the abstraction of a chlorine atom from CCl_4.[39]

Scheme III



11

Although dimerization of phenyl radicals or diazonium salts to form biphenyls is well-established,[42] no 6–6' purine dimers have been reported. Under appropriate conditions, it may be possible to produce 6–6' dimeric purines such as 11 (Scheme III).[43] Products corresponding to donation of the 1' or 4' hydrogen atoms of ribose have not been observed, although hydrogens at these sites correspond to the easily abstractable α-H atoms in tetrahydrofuran. Similarly, radical combination to produce 6-alkoxypurine was not observed.

The explanation for the failure of conventional reductive deamination methods with purines (e.g., $NaNO_2$ in aqueous acetic acid or HCl) presumably centers around attack of the intermediate diazonium compound by water, producing the hypoxanthine (Scheme I). Such aqueous deamination to form hypoxanthines has become a common method for preparing them. Although 1 equiv of water is produced under the conditions of our reactions here (Scheme II), no hypoxanthine products have been noted.[44] Apparently the rate of decomposition to form purinyl radicals by the diazonium or azo intermediate is much greater than the rate of attack by water upon the diazonium intermediate, or the extent of reaction of purinyl radical with the solvent is very much greater than the extent of reaction between the radical and water to generate hypoxanthine products.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra employing tetramethylsilane as an internal standard were recorded on a Bruker Model HX90E Pulse Fourier transform spectrometer and also on a Varian A-60 spectrometer. Low-resolution mass spectra were obtained on a Hitachi RMU-6 mass spectrometer. The ultraviolet spectra were obtained on a Varian Cary Model 219 spectrophotometer. Tetrahydrofuran was distilled over calcium hydride prior to use and stored over 4-Å molecular sieves under nitrogen. *n*-Pentyl nitrite[45] was dried over sodium sulfate, distilled, and stored at 10 °C over 4-Å molecular sieves. Carbon tetrachloride and bromoform were distilled prior to use. Diiodomethane was used without purification. Di-

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(37) Nair, V.; Emanuel, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 1571.
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(39) Cadogan, J. I. G.; Hey, D. H.; Hibbert, P. G. *J. Chem. Soc.* **1965**, 3939.
(40) Dinaburg, M. S. "Photosensitive Diazo Compounds and Their Uses"; Focal Press: London and New York, 1964.
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(42) Cohen, T.; LeWarchik, R. J.; Tarino, J. Z. *J. Am. Chem. Soc.* **1974**, *96*, 7753 and references therein.
(43) When 6-iodo-9-ethylpurine is heated and/or photolyzed, a crystalline compound, which is possibly the dimer 11, R = C_2H_5, is isolated.
(44) When 2',3',5'-tri-*O*-acetylcytidine is reacted under similar conditions to effect replacement of NH_2 by H, Cl, Br, and I, good yields of the corresponding uridine are obtained in all cases. In the cytidyl case, the pyrimidine base possesses little or no aromatic stability due to N-alkyl substitution. Reaction may proceed via an ionic mechanism where generated water serves as the nucleophile. Extension of the bromination reaction to aromatic 2-aminopyrimidine, however, results in isolation of 52.8% 2-bromopyrimidine.
(45) "Vogel's Textbook of Practical Organic Chemistry", 4th ed.; Furniss, B. S., et al., Eds.; Longman: London, 1978; p 409.

Table IV. Method and Yields in Deamination Reactions

no.	compd	RONO equiv	% yield	mp, °C
1b	2′,3′,5′-triacetylnebularine	20	45.8	oil
3b	2′,3′,5′-triacetyl-6-chloronebularine	2.24	65.5	oil
3b	2′,3′,5′-triacetyl-6-chloronebularine	20	71.8	
4b	2′,3′,5′-triacetyl-6-bromonebularine	2.24	55.8	oil
4b	2′,3′,5′-triacetyl-6-bromonebularine	20	72.7	
5b	2′,3′,5′-triacetyl-6-iodonebularine	20	68.6	oil
7	9-ethylpurine	method A	21	51-53
7	9-ethylpurine	20	68.2	
8	6-chloro-9-ethylpurine	2.24	68.1	79-80
8	6-chloro-9-ethylpurine	40	65.3	
9	6-bromo-9-ethylpurine	2.24	37.9	94
9	6-bromo-9-ethylpurine	20	56.8	
10	6-iodo-9-ethylpurine	2.24	23.7	142
10	6-iodo-9-ethylpurine	20	35.2	

methylformamide was dried over barium oxide (72 h), distilled, and stored over 4-Å molecular sieves. Starting purines and purine nucleosides were dried prior to use. Dixylylethane was provided courtesy of Gulf Oil Chemicals and used without purification. Preparative layer chromatography was carried out on EM silica gel PF_{254} plates.

9β-D-Ribofuranosylpurine (Nebularine, 1a). Under a nitrogen atmosphere, 0.393 g (1.0 mmol) of desiccated **2b**[34] in 20 mL of dry tetrahydrofuran was added over 20 min to a stirred refluxing solution of 2.7 mL (20 mmol) of *n*-pentyl nitrite in 20 mL of THF. Constant illumination during reflux was provided by an unfrosted 200-W tungsten lamp supported 2 in. from the apparatus. Gas evolution began. Reflux was continued for 96 h. The final reaction mixture was yellow-orange. Solvent was removed on a rotary evaporator. The residue was dissolved in 1:9 methanol–dichloromethane, dried (Na_2SO_4), and chromatographed on preparative silica gel plates with 1:19 ethanol–chloroform as developing solvent. The band at R_f 0.28 gave 0.173 g of 9β-(2′,3′,5′-tri-*O*-acetyl)-D-ribofuranosylpurine, **1b** (0.458 mmol, 45.8%), as a pale yellow oil:[6] ^{13}C NMR, see Table I; ^1H NMR (Me_4Si, $CDCl_3$) δ 2.09 (s, 1 H), 2.11 (s, 1 H), 2.17 (s, 1 H), 4.45 (s, 2 H), 5.73 (t, 1 H), 6.03 (t, 1 H), 6.33 (d, 1 H), 8.40 (s, 1 H), 9.01 (s, 1 H), 9.18 (s, 1 H). To 0.795 g (2.1 mmol) of triacetylnebularine (**1b**) was added saturated methanolic ammonia[5] at 0 °C to give, following recrystallization from methanol, 0.159 g (0.63 mmol, 31.5%) of **1a** as tan crystals: mp 178–179 °C [lit.[5] mp 181–182 °C]; ^{13}C NMR, see Table I; ^1H NMR δ Me_4Si (D_2O) 3.85 (d, 2 H), 4.1–4.9 (m, 3 H), 6.1 (d, 1 H), 8.63 (s, 1 H), 8.81 (s, 1 H), 8.97 (s, 1 H); UV, see Table III.

6-Amino-9-ethylpurine (9-Ethyladenine, 6). To a suspension of 5.07 g of adenine (37.5 mmol) in 80 mL of dimethylformamide was added 1.8 g (37.5 mmol) of a 50% dispersion of sodium hydride in mineral oil at room temperature with moisture protection. The reaction mixture was stirred for 30 min and the resulting white mass of sodium adeninide was warmed to 60 °C for an additional 30 min. A solution of 7.5 g (37.5 mmol) of ethyl *p*-toluenesulfonate[46] in 10 mL of DMF was added over 10 min at 25 °C to the sodium adeninide, and the mixture was stirred for an additional 10 min and warmed to 60 °C for 10 h. The solvent was removed on a rotary evaporator, and the residue was dissolved in 100 mL of 1:9 methanol–dichloromethane. Insoluble sodium *p*-toluenesulfonate was filtered off. After removal of solvent from the filtrate, recrystallization of the portion soluble in hot 2-butanone gave 2.45 g (15 mmol, 40%) of **6** as a fine white powder: mp 192–193 °C [lit.[11] mp 194–195 °C]; ^{13}C NMR (Me_4Si, $CDCl_3$) δ 15.5, 38.9, 120.1, 139.9, 150.3, 153.1, 155.8; ^1H NMR (Me_4Si, Me_2SO-d_6) δ 1.40 (t, 3 H), 4.20 (q, 2 H), 7.05–7.3 (br s, 2 H), 8.18 (s, 2 H); UV (H_2O) λ_{max} 262 nm (ε 1.3 × 10^4).

Anal. Calcd for $C_7H_9N_5$: C, 51.5; H, 5.5; N, 42.9. Found: C, 50.9; H, 5.5; N, 43.1.

9-Ethylpurine (7). Method A. From Purine. To 0.72 g (6.0 mmol) of purine dissolved in 15 mL of dimethylformamide was added with stirring under moisture protection 0.288 g (6.0 mmol) of a 50% dispersion of sodium hydride in mineral oil. After gas evolution ceased, the solution was heated to 50 °C for 45 min. After the solution was cooled to 0–5 °C, a solution containing 1.2 g (6.0 mmol) of ethyl *p*-toluenesulfonate[46] in 5 mL of dimethylformamide was added rapidly. The reaction vessel was allowed to warm to 25 °C and stirred for 10 h. Solvent was removed (<35 °C) at reduced pressure and sodium *p*-toluenesulfonate was removed as for **6**. Preparative layer chromatography on silica gel using 1:9 methanol–dichloromethane for development gave 0.186 g (1.26 mmol, 21%) of **7** (mp 44–48 °C). Sublimation at 60 °C under aspirator vacuum yielded a flocculent white sublimate of **7**, mp 51–53 °C [lit.[11] mp 53–56 °C].

Method B. From 6. A solution of 0.163 g (1.0 mmol) of **6** was dissolved in 30 mL of tetrahydrofuran and added slowly to a refluxing solution of 2.7 mL (20 mmol) of *n*-pentyl nitrite in 30 mL of tetrahydrofuran, as in **1b**. After 5 h, the reaction was worked up as before and chromatographed on silica gel, using 1:9 methanol–dichloromethane. Upon elution the band at R_f 0.26 yielded 0.101 g (0.682 mmol, 68.2%) of crude **7**, as a pale yellow material which was identical in all respects with that obtained by alkylation of purine in method A.

Method C. From 6. The procedure of method B was repeated with 20 mL of 1,1′-ethylidenebis(3,4-dimethylbenzene)[33] (dixylylethane) in place of tetrahydrofuran. After 1 h at 100 °C a solution formed. Heat and light were continued for an additional 18 h. The reaction mixture was placed on a column consisting of 60–200 mesh silica gel and flushed with hexane (100 mL). The column was then eluted with 1:9 methanol–methylene chloride. Preparative layer chromatography of the evaporated eluant as before gave 0.056 g (0.375 mmol, 37.5%) of **7**, identical in all respects with the product from method B: ^{13}C NMR, see Table I; ^1H NMR, see Table II; UV, see Table III; mass spectrum, *m/z* 148 (M^+), 133, 120, 106, 93, 66.

Anal. Calcd for $C_7H_8N_4$: C, 56.8; H, 5.4; N, 37.8. Found: C, 56.6; H, 5.4; N, 38.2.

6-Chloro-9-ethylpurine (8). Method A. From 6-Chloropurine. 6-Chloropurine, 1.08 g (7.0 mmol), was converted by the method of Montgomery and Temple[10] in dimethyl sulfoxide with potassium carbonate and ethyl iodide to give **8** as an oil which solidified upon chilling. The solid product was recrystallized once from Skellysolve C to give a fluffy white solid, 0.55 g (3.01 mmol, 43%), mp 78–80 °C [lit.[10] mp 81–84 °C].

Method B. From 6. A mixture of 0.163 g (1.0 mmol) of **6**, 40 mL of carbon tetrachloride, and 0.3 mL (2.24 mmol) of *n*-pentyl nitrite was reacted as for **3b**, except that the system here was heated to reflux temperature (see Table IV). After 12 h, the brown reaction mixture was worked up as before and chromatographed on silica gel, using 1:9 methanol–dichloromethane. From the band at R_f 0.53 was obtained, after elution, 0.124 g (0.681 mmol, 68.1%) of **8**, which was recrystallized from Skellysolve C to give a fluffy white solid identical in every respect with **8** isolated from method A: mp 78–80 °C, which showed no depression upon mixture with material from method A; ^{13}C NMR, see Table I; ^1H NMR see Table II; UV, see Table III; mass spectrum, *m/z* 184 ($^{37}ClM^+$), 182 ($^{35}ClM^+$), 156, 154, 129, 127, 119, 92.

Anal. Calcd for $C_7H_7N_4Cl$: C, 46.0; H, 3.8; N, 30.7. Found: C, 45.6; H, 3.9; N, 29.3.

6-Bromo-9-ethylpurine (9). To 0.163 g (1.0 mmol) of **6** were added 2.7 mL (20 mmol) of *n*-pentyl nitrite and 10 mL of bromoform. The resulting suspension was reacted as for **3b**, except

(46) Tipson, R. S. *J. Org. Chem.* **1944**, *9*, 235. Purification was facilitated by washing a CH_2Cl_2 solution of crude product through a 2-in. barrel of 80–200 mesh silica gel and subsequently removing the solvent.

that the mixture was slowly warmed from 60 to 120 °C. After 3 h the reaction was worked up as before. Development of preparative layer plates with 1:9 methanol–dichloromethane gave a trace of starting **6** and 0.129 g (0.568 mmol, 56.8%) of **9**, which was recrystallized from 10 mL of Skellysolve C to give white scales of **9**: mp 93–95 °C; ^{13}C NMR, see Table I; ^{1}H NMR, see Table II; UV, see Table III; mass spectrum, m/z 228 ($^{81}BrM^+$), 226 ($^{79}BrM^+$), 199, 197, 147, 119, 92, 65.

Anal. Calcd for $C_7H_7N_4Br$: C, 37.0; H, 3.1; N, 24.7. Found: C, 37.4; H, 3.2; N, 24.6.

6-Iodo-9-ethylpurine (10). A mixture of 0.163 g (1.0 mmol) of **6** and 2.7 mL (20 mmol) of *n*-pentyl nitrite was treated with 5 mL of diiodomethane as in **5b** and warmed to 80 °C. After 10 h, the reaction was worked up and treated to remove iodine color as before. Preparative layer chromatography on silica gel (1:9 methanol–methylene chloride for development) gave at R_f 0.49 0.0964 g (0.345 mmol, 34.5%) of **10**, which was recrystallized from Skellysolve C to give a dense pale yellow powder: mp 141–143 °C; ^{13}C NMR, see Table I; ^{1}H NMR, see Table II; UV, see Table III; mass spectrum, m/z 274 (M^+), 147, 119, 92, 65.

Anal. Calcd for $C_7H_7N_4I$: C, 30.7; H, 2.6; N, 20.5. Found: C, 31.5; H, 2.7; N, 20.0.

6-Chloro-9β-(2′,3′,5′-tri-*O*-acetyl)-D-ribofuranosylpurine (3b). Under a nitrogen atmosphere, 0.393 g (1.0 mmol) of dry **2b** was added to a solution of 0.3 mL (2.24 mmol) of *n*-pentyl nitrite in 40 mL of carbon tetrachloride. The suspension was stirred and illuminated as for **1b** and warmed to 80 °C. Reaction was discontinued after 23 h and the red-brown mixture, worked up as for **1b**, gave, after development of preparative layer plates with 1:9 methanol-methylene chloride, 0.270 g of **3b** (0.656 mmol, 65.5%) as a yellow oil (R_f 0.58). Recovery of 0.093 g (0.236 mmol, 23.6%) of **2b** was made. Similar reaction using 2.7 mL (20 mmol) of *n*-pentyl nitrite gave a trace of starting compound **2b** (R_f 0.27) and 0.296 g (0.718 mmol, 71.8%) of **3b**: ^{13}C NMR, see Table I; ^{1}H NMR, see Table II; UV, see Table III.

Anal. Calcd for $C_{16}H_{17}N_4O_7Cl\cdot H_2O$: C, 44.6; H, 4.4; N, 13.0. Found: C, 43.9; H, 4.2; N, 11.9.

6-Bromo-9β-(2′,3′,5′-tri-*O*-acetyl)-D-ribofuranosylpurine (4b). A mixture of 0.393 g (1.0 mmol) of **2b**, 2.7 mL (20 mmol) of *n*-pentyl nitrite, and 15 mL of bromoform was reacted as for **1b**, with the solution maintained at 80 °C. The reaction mixture turned a golden color; gas evolution ceased and reaction was stopped after 3.5 h. After workup using 1:9 methanol–dichloromethane as developing solvent for silica gel preparative layer plates, 0.030 g (0.077 mmol, 7.7%) of **2b** was recovered (R_f 0.30) and 0.332 g (0.727 mmol, 72.7%) of **4b** was isolated as a pale yellow oil (R_f 0.59): ^{13}C NMR, see Table I; ^{1}H NMR, see Table II; UV, see Table III.

Anal. Calcd for $C_{16}H_{17}N_4O_7Br\cdot H_2O$: C, 40.4; H, 3.6; N, 11.8. Found: C, 40.6; H, 3.8; N, 11.6.

6-Iodo-9β-(2′,3′,5′-tri-*O*-acetyl)-D-ribofuranosylpurine (5b). A mixture of 0.393 g (1.0 mmol) of **2b** and 2.7 mL (20 mmol) of *n*-pentyl nitrite was stirred at 60 °C under nitrogen. Diiodomethane (5 mL) was added at once, under illumination as for **1b**, with stirring. After 2 h the red reaction mixture was cooled and worked up as before except that the methylene chloride solution of the residue was treated with saturated aqueous sodium sulfite solution to remove the free iodine before drying. Development with 1:9 methanol–methylene chloride gave a 0.056-g (0.143 mmol, 14.3%) recovery of **2b** (R_f 0.30) and 0.346 g (0.686 mmol, 68.6%) of **5b**, as a yellow oil which darkens upon standing (R_f 0.61): ^{13}C NMR, see Table I; ^{1}H NMR, see Table II; UV, see Table III; mass spectrum, m/z 504 (M^+).

Anal. Calcd for $C_{16}H_{17}N_4O_7I$: C, 38.1; H, 3.4; N, 11.1. Found: C, 38.3; H, 3.5; N, 11.0.

Registry No. 1a, 550-33-4; **1b**, 15981-63-2; **2b**, 7387-57-7; **3b**, 5987-73-5; **4b**, 74465-47-7; **5b**, 5987-74-6; **6**, 2715-68-6; **7**, 5427-23-6; **8**, 5462-86-2; **9**, 74465-48-8; **10**, 74465-49-9; adenine, 73-24-5; sodium adeninide, 40428-86-2; purine, 120-73-0; 6-chloropurine, 87-42-3.

Macro Rings. 49. Use of Transannular Reactions to Add Bridges to [2.2]Paracyclophane[1,2]

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New transannular reactions were used to introduce additional bridges into [2.2]paracyclophane (**1**). With CH_2O–HCl, 4-acetyl[2.2]paracyclophane (**3**) gave (55%) 4-acetyl-13-(chloromethyl)[2.2]paracyclophane (**4**), whose substituents are pseudogem to one another. With $AgNO_3$–*t*-BuOK, **4** gave (84%) 1-keto[3.2.2](1,2,5)cyclophane (**5**), reduction of which produced (78%) [3.2.2](1,2,5)cyclophane (**6**). Treatment of **4** with NaOBr gave a mixture (90%) of *pseudogem*-carboxy(hydroxymethyl)[2.2]paracyclophane (**7**) and *pseudogem*-aldehydocarboxy[2.2]-paracyclophane (**8**), each of which was isolated and characterized. Oxidation of the mixture with $KMnO_4$ gave (70%) *pseudogem*-dicarboxy[2.2]paracyclophane (**9**), whereas reduction with $LiAlH_4$ produced (72%) *pseudogem*-bis(hydroxymethyl)[2.2]paracyclophane (**10**). With PBr_3, **10** gave (81%) *pseudogem*-bis(bromomethyl)-[2.2]paracyclophane (**11**), which with Na_2S gave (39%) 2-thia[3.2.2](1,2,5)cyclophane (**12**). With Ag_2O, **11** produced 26% each of *pseudogem*-aldehydomethyl[2.2]paracyclophane (**13**) and 2-oxa[3.2.2](1,2,5)cyclophane (**14**). With TsOH–AcOH, diol **10** gave 82% of aldehyde **13** and 13% of ether **14**. With BF_3·$O(Et)_2$, **14** rearranged to **13** (89%). Butyllithium mixed with dibromide **11** gave (65%) [2.2.2](1,3,5)cyclophane (**2**). The tosylhydrazone of aldehyde **13** (compound **17**), when heated with $NaOCH_3$ or irradiated, also gave **2** (71 and 85%, respectively). Comparisons of the ^{1}H NMR and UV spectra of hydrocarbons **1**, **2**, and **6** suggest that **2** is more rigid and strained than the other two. When heated with dimethyl acetylenedicarboxylate, **2** formed a 1:1 Diels–Alder adduct (**19**, 68%) involving the 5,8-positions of **2**, whereas with **1** or **6**, no such reaction occurred. That **2** is aromatic is illustrated by the fact that with AcCl–$AlCl_3$ it acetylated to give (79%) 6-acetyl[2.2.2](1,3,5)cyclophane (**20**). When heated with thiophenol, a good H· donor, **1** gave *p,p′*-dimethylbibenzyl (71%). When similarly treated, **2** gave (88%) 5,14-dimethyl[2.2](1,2)cyclophane (**22**). When heated at 220 °C with diethyl fumarate or maleate, **2** cycloadded across the benzyl–benzyl bond remote from the other two bridges to give (51 and 42%, respectively) a diastereomeric mixture of 2,3-bis(carboethoxy)[4.2.2](1,3,4)cyclophanes (**23**). The unusual reactions of the pseudogem-disubstituted [2.2]paracyclophanes are discussed in terms of proximity effects. The unusual spectral and reactivity effects of [2.2.2](1,2,5)cyclophane are interpreted in terms of compression and bent benzene effects.

Diparaxylylene was first obtained in 1949 by the extraction of polymer prepared by pyrolysis of *p*-xylene.[4] It was identified and characterized solely by its X-ray structure (later corrected),[5] melting point, and insolubility.[4]

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