Anal. Calcd for $C_{14}H_{19}N_5O_3$: C, 55.07; H, 6.27; N, 22.94. Found: C, 55.28; H, 6.59; N, 22.88.

Cyclonucleoside Analog (33). A solution of 336 mg of **32**, 5 ml of dry pyridine, and 231 mg of *p*-toluenesulfonyl chloride was prepared at 0° and stirred at room temperature for 22 hr. The mixture, containing a precipitate, was cooled to 0°, diluted with 1 ml of H_2O and with 15 ml of saturated aqueous $NaHCO_3$, and extracted with $CHCl_3$ (four 15-ml portions) and with benzene (two 20-ml portions). The organic extracts were combined, filtered, dried (Na_2SO_4), and concentrated to a solid residue (228 mg, 45%). The residue, presumably the *p*-toluenesulfonate of **32**, was heated in 15 ml of refluxing dioxane for 1 hr to effect cyclization. The white solid that was filtered from the cooled mixture and dried at 70° *in vacuo* weighed 157 mg (31%); mp 328–330° dec (MT). Recrystallization from acetonitrile (50 ml) and water (1 ml) and similar drying gave 57 mg of **33**: mp 352–354° dec (MT); uv λ_{max} in mμ ($\epsilon \times 10^{-3}$) 272 (14.9) in 0.1 *N* HCl and at pH 7, 272 (9.2) in 0.1 *N* NaOH.

Anal. Calcd for $[C_{14}H_{18}N_5O_2]^+[C_7H_7SO_3]^-$: C, 54.89; H, 5.48; N, 15.24; S, 6.98. Found: C, 55.08; H, 5.46; N, 15.25; S, 7.0.

Additional **33** was isolated by evaporating the aqueous $NaHCO_3$ layer to dryness and leaching the residue with hot acetonitrile. The residue remaining after evaporation of acetonitrile was heated in refluxing dioxane for 1 hr. Filtration gave 65 mg of solid, mp 330–335° dec (MT), identified as crude **33** by its ir and uv spectra.

(±)-9-[β-(2α,3α-Dihydroxy-4β-(hydroxymethyl)cyclopentyl)]hypoxanthine (30). A solution of 3.45 g of **27** hydrochloride in 100 ml of 1 *N* HCl was heated under reflux for 3.5 hr, cooled, and concentrated *in vacuo* to a syrup from which several portions of H_2O were evaporated. A solution of the residue in 100 ml of H_2O was stirred with 20 g of the carbonate form of a basic resin (Dowex 1-8X, CO_3^{2-}). Since the solution was still acidic, portions of the basic resin (OH^- form) were added until the pH was 5–6. The filtrate (plus washings) from the resin was treated with activated carbon and concentrated *in vacuo* to a white solid, which was triturated with ethanol. The product was filtered from the cold mixture, washed with ethanol, and dried (P_2O_5) *in vacuo* at 60°: yield 1.64 g (57%); mp 222–225° dec (MT). Recrystallization from water–ethanol gave pure **30**: mp 225–227° dec (MT); uv λ_{max} in mμ ($\epsilon \times 10^{-3}$) 250 (11.4) in 0.1 *N* HCl, 249 (12.1) at pH 7, 254 (13.0) in 0.1 *N* NaOH; ir (cm^{-1}) 1695 (C=O).

Anal. Calcd for $C_{11}H_{14}N_4O_4$: C, 49.62; H, 5.30; N, 21.04. Found: C, 49.30; H, 5.36; N, 20.93.

Compound **30** was also prepared by treating the adenine derivative **28** with sodium nitrite and acetic acid and was isolated by elution from a basic resin column with 25% aqueous acetic acid.

(±)-9-[β-(2α,3α-Dihydroxy-4β-(hydroxymethyl)cyclopentyl)]-9H-purine-6(1H)-thione (31). A mixture of 1.0 g of **27** hydrochloride, 304 mg of thiourea, and 20 ml of 1-propanol was heated under reflux for 2 hr. Chilling and filtering the mixture afforded 650 mg (65%) of tan solid, mp 225–228° dec (MT), that analyzed as a hydrochloride.

Anal. Calcd for $C_{11}H_{14}N_4O_3S \cdot HCl$: C, 41.44; H, 4.74; Cl, 11.13; N, 17.57; S, 10.06. Found: C, 41.61; H, 4.79; Cl, 10.8; N, 17.55; S, 9.6.

A solution of 374 mg of the hydrochloride in water (7 ml) was adjusted to pH 5 with base, the cream-colored precipitate (239 mg in two crops) was washed with H_2O, recrystallized from H_2O, and dried at 110° *in vacuo:* mp 265–267° dec (MT); uv λ_{max} in mμ ($\epsilon \times 10^{-3}$) 323 (22.0) and 224 (9.6) in 0.1 *N* HCl, 321 (23.0) and 225 (10.4) at pH 7, 311 (23.0) and 232 (14.3) in 0.1 *N* NaOH.

Anal. Calcd for $C_{11}H_{14}N_4O_3S \cdot 0.25H_2O$: C, 46.06; H, 5.09; N, 19.53; S, 11.19. Found: C, 46.27; H, 5.14; N, 19.49; S, 10.77.

(±)-9-[β-(2α,3α-Dihydroxy-4β-(hydroxymethyl)cyclopentyl)]-6-(methylthio)purine (29). A mixture of 160 mg of **31** hydrochloride, 1.0 ml of 1.0 *N* NaOH, 1.0 ml of H_2O, and 0.2 ml of methyl iodide was stirred at room temperature for 4 hr and then evaporated *in vacuo* to dryness. The residue was dissolved in hot ethanol, the mixture cooled, and 20 mg of sodium halides removed by filtration. The filtrate was evaporated to a syrup, and the remaining sodium iodide and trace impurities were removed by column chromatography on silica gel (elution with 95:5 $CHCl_3$–CH_3OH). The product-containing fraction was evaporated to a foam that was induced to solidify by adding and evaporating ethyl acetate: yield of white product, 91 mg (61%); mp 172–175° (MT); uv λ_{max} in mμ ($\epsilon \times 10^{-3}$) 303 (sh), 295 (17.1), 290 (sh), 221 (11.5) in 0.1 *N* HCl; 293 (18.3), 286 (18.7), 221 (11.8) in 0.1 *N* NaOH and at pH 7.

Anal. Calcd for $C_{12}H_{16}N_4O_3S$: C, 48.63; H, 5.44; N, 18.91; S, 10.82. Found: C, 48.76; H, 5.52; N, 18.63; S, 11.10.

Acknowledgment. The authors are indebted to Drs. W. J. Barrett, P. D. Sternglanz, and associates of this Institute for microanalytical data; to Dr. W. C. Coburn, Jr., Mrs. Martha Thorpe, and associates of this Institute for spectral determinations; and to Dr. J. A. Montgomery for encouragement. Some of the microanalyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

Communications to the Editor

Remote Oxidation of Unactivated Methylene Groups

Sir:

Nature's ability to carry out selective functionalization of simple substrates (*e.g.* stearic → oleic acid) utilizes a principle of great power which has not been applied by chemists: any intrinsic reactivity of the substrate, dictated by its own functional groups, can be overridden by combining the substrate with a reagent (*i.e.*, the enzyme) whose selectivity is dominant. In particular, even a single unactivated CH_2 group of a chain can be attacked selectively within an enzyme–substrate complex by steric approximation to the attacking atom. We wish to report the first chemical example of the application of this principle.

As the reagent to attack an unactivated CH_2 group we selected benzophenone triplet.[1] After hydrogen atom transfer the resulting pair of radicals, still held together by the link between reagent and substrate, should couple as in the Yang reaction;[2] it should be noted, however, that in contrast to the four-membered products of the Yang reaction our products (II) have rings of 20 and more members. A series of *p*-benzophenonecarboxylic esters (I)[3] of long-chain alcohols was prepared; the reversible ester link attaches the reagent benzophenone to the substrate alcohol at a site remote from that involved in subsequent chemistry. Irradiation of 10^{-3} *M* solutions of the esters I in CCl_4 with a 450-W Hanovia medium-pressure mercury lamp using a uranium glass filter led to rapid (quantum yield ~0.2) disappearance of the benzophenone chromophore. The crude alcohol product II was dehydrated

(1) C. Walling and M. J. Gibian, *J. Am. Chem. Soc.*, 87, 3361 (1965).

(2) N. C. Yang and D. H. Yang, *ibid.*, 80, 2913 (1958).

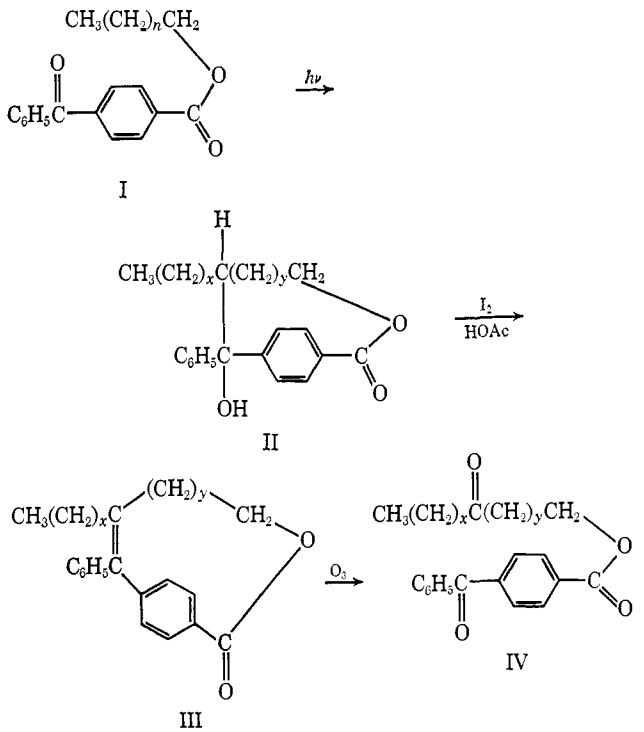
(3) All compounds had mass, nmr, and infrared spectra consistent with the assigned structures.

Table I. Per Cent Oxidation

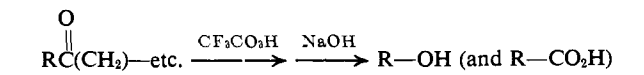
Oxidation site	Number of carbons in ester alkyl chain: C-14	C-16[d]	C-16[d]	C-18	C-20
C-8					
C-9	1.4	1.1	1.4	0.1	<2
C-10	3	7.8	8	8	5
C-11	11	12	10	17 ± 3[c]	15
C-12	49[a]	13	8	21	20
C-13	22[b]	10	3	18	19 ± 3[c]
C-14	0	56[a]	66[a]	12	19
C-15		7[b]	10[b]	5	13
C-16		0	0	13[a]	8
C-17				6[b]	0.7
C-18				0	0
C-19					0[b]
C-20					

[a] Measured amount of ethanol doubled in accord with selectivity against ethyl migration in the Baeyer–Villiger reaction. Not corrected for steam distillation work-up, making these values minimum values. [b] Measured by nmr analysis of IV. [c] Reproducibility of measurements within one experiment at least ±1% except where noted. [d] Typical reproducibility between completely different runs.

to olefin III with I_2–HOAc at reflux for 30 min. The olefin was then ozonized in CH_3OH, followed by CH_3SCH_3 treatment, and the total diketone material IV was collected. In some cases the mixture crystallized at this point to afford up to 40% over-all of crystalline IV and 60% of chromatographically homogeneous IV. We could also hydrolyze IV to the keto alcohols. However, in order to determine the selectivity of functionalization we analyzed the total product IV without fractionation.



Baeyer–Villiger oxidation of the mixture IV with trifluoroperacetic acid in $CHCl_3$ was followed by saponification and aqueous distillation of the straight-chain alcohol products. Vapor-phase chromatographic analysis of the alcohol mixture gives an indication of the position of the new carbonyl group in IV. It was



assumed that the amount of C_n alcohol is directly proportional to the amount of IV which has its new carbonyl group on the $n + 1$ carbon from the end; however, Baeyer–Villiger oxidation selects strongly against methyl migration, and, we have found, it is somewhat selective against ethyl migration as well (3-heptanone affords 2:1 butyl propionate–ethyl pentanoate). Accordingly the amount of methyl ketone in IV was determined by integration of the nmr singlet at δ 1.96, and the amount of ethyl ketone was calculated from the ethanol peak after correction for the apparent 2:1 selectivity. The amount of C_{n-2} oxidation is still underestimated by these data, due to problems in quantitative recovery of ethanol. The results are listed in Table I.

As can be seen from Table I, functionalization does not occur below C-9 due to inaccessibility, the terminal methyl groups are not attacked, and the penultimate carbon has a decreased reactivity as well.[4] In the case of the 16-carbon substrate there is considerable selectivity for C-14, even more if the analytical losses of ethanol are corrected for. Obviously if the substrate were also a rigid molecule, *e.g.*, a steroid, one might expect greatly increased selectivity. We are exploring this, as well as the interesting changes in selectivity of our present system as a function of solvent. However, our observations to date indicate that intramolecular hydrogen abstraction can occur over very large distances, much further than the six atoms in such processes as the Yang,[2] Barton,[5] and Hofmann–Loeffler[6] reactions. Accordingly, the possibility of developing a variety of specific functionalization reactions utilizing this principle is at hand.[7]

(4) *Cf.* P. Smit and H. J. den Hertog, *Rec. Trav. Chim.*, **83**, 891 (1964), for a related observation.
(5) D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechet, *J. Am. Chem. Soc.*, **82**, 2640 (1960); see also ref 1 and 2 therein.
(6) W. A. Pryor, "Free Radicals," McGraw-Hill Book Co., Inc., New York, N. Y., 1966, p 280 ff.
(7) Support of this work by the National Institutes of Health is gratefully acknowledged.
(8) Public Health Service Predoctoral Fellow.

Ronald Breslow, Mitchell A. Winnik[8]

Department of Chemistry, Columbia University
New York, New York 10027

Received February 14, 1969