simple alkyl free radicals at a rate at or near the diffusion-controlled limit.[5]

Fortunately a distinction between these two mechanisms can be readily achieved experimentally. If one focuses on the process by which the intermediates in the two mechanisms are diverted to carbene products (trimethylcyclopropane and *tert*-butylethylene) on the one hand and reduction product (2,2-dimethylbutane) on the other, one discerns a basic difference in the two mechanisms. In the mechanism presented in Scheme I, this partitioning takes place by divergent reactions of the carbenoid intermediate itself and is not dependent at the point of partition on further involvement of the reducing agent, **1**. More explicitly, the intermediate carbenoid is diverted from yielding carbenoid products by protonation, a reaction not dependent on radical anion concentration.[8] In the mechanism outlined in Scheme II, however, the carbene intermediate is diverted from conversion to carbene products only by further reduction, a process first order in sodium naphthalene (**1**) concentration.

Thus, Scheme I predicts that the ratio of carbene products to reduction product should be independent of the concentration of sodium naphthalene (**1**) employed, whereas Scheme II predicts that increasing the concentration of **1** should result in progressively higher yields of reduction product relative to carbene product. Experimentally, the mole ratio of 2,2-dimethylbutane to trimethylcyclopropane plus *tert*-butylethylene produced varied from 0.03 to 3.4 as the concentration ratio of 2,2-dichloro-3,3-dimethylbutane to sodium naphthalene employed was decreased from 10 to 0.1.[9] It is significant, furthermore, that over this entire range the ratio of *tert*-butylethylene to trimethylcyclopropane did not vary by more than 5%. These results, while inconsistent with the mechanism outlined in Scheme I, are wholly consistent with that set forth in Scheme II. Further evidence in refutation of Scheme I is provided by our failure to find any indication of the presence of 2-chloro-3,3-dimethylbutane in a reaction mixture to which insufficient sodium napthhalene had been added to effect complete reduction of the starting dihalide.

Additional circumstantial evidence for the formation of carbene radical anions in the reaction of geminal dihalides with sodium naphthalene (**1**) derives from experiments conducted with the methylene halides as substrates. Since intramolecular carbene (carbenoid) products clearly result from reaction of **1** with both 2,2-dichloro-3,3-dimethylbutane and 1,1-dichloropropene, one would expect to be able to trap intermolecularly the methylene generated by reaction of **1** with a methylene halide. Reaction of CH_2Cl_2 with **1** in 40:60 (v/v) DME–cyclohexene does yield trace amounts of norcarane, but in no case have we been able to obtain this methylene addition product in greater than 0.4% yield. This result is explicable if the methylene generated is, in fact, reduced to the methylene radical anion H_2C^- at a rate rapid relative to that for addition of methylene to cyclohexene. The character and relative yield of the low molecular weight products which are formed in high yield in this reaction are wholly consistent with this hypothesis.[10]

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(8) This argument would be vitiated, of course, if 2-chloro-3,3-dimethylbutane were in rapid equilibrium with the carbenoid. This seems most unlikely, however, in the case of a simple alkyl chloride in the presence of the relatively weak bases (**1**, CH_3O^-) present in any significant concentration in the reaction medium.

(9) Since this reaction is macroscopically instantaneous, the significant variable is the mole ratio at the moment of mixing. The highest mole ratio of dihalide was obtained by injecting 4 ml of *ca.* 0.1 *M* **1** into 0.1 ml of 1 *M* dihalide solution. The lowest mole ratio of dihalide was obtained by injecting 3 ml of *ca.* 1 *M* **1** into 1 ml of 0.1 *M* dihalide solution. In this manner the volume of solvent and the number of moles of dihalide were held constant, and all reactions were carried to completion. Products **4**, **5**, and **6** were shown to be stable to excess sodium naphthalene.

(10) The details of this investigation will be described in a forthcoming publication.

(11) National Science Foundation Undergraduate Research Participant.

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Epimerization in the Preparation of Purine Nucleosides by the Fusion Reaction[1]

Sir:

Because of its convenience, the fusion reaction of Sato, *et al.*,[2] for the preparation of purine and pyrimidine nucleosides has gained favor over the established mercuri procedure of Davoll,[3] even though it is less stereospecific, often resulting in the formation of a significant quantity of the cis as well as the expected trans nucleosides[4–9] and, less frequently, of 7- as well as 9-glycosylpurines.[7,10]

We now wish to report the results of the acid-catalyzed fusion of a new *ribo*-hexofuranose with 2,6-dichloropurine. 1,2:5,6-Di-*O*-isopropylidene-α-D-allofuranose (**1**)[11] was selectively hydrolyzed to 1,2-*O*-isopropylidene-α-D-allofuranose (**2**), which was oxidized with metaperiodate to 1,2-*O*-isopropylidene-α-D-*ribo*-pento-1,5-dialdo-1,4-furanose (**3**). Reaction of **3** with carbethoxymethylenephosphorane in tetrahydrofuran gave a mixture of *cis*- and *trans*-ethyl 5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*ribo*-heptofuran-5-enuronate (**4**), which was reduced with diimide to ethyl 5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*ribo*-heptofuranuronate (**5**). Treatment of **5** with acetic anhydride, glacial acetic acid, and concentrated sulfuric acid[12] gave, in an overall yield of 67% from **1**, ethyl 1,2,3-tri-*O*-acetyl-5,6-dideoxy-D-*ribo*-heptofuranuronate (**6**): nmr δ 1.25 (t, 3, CH_3CH_2O), 1.5–2.8 (m, 13, CH_2CH_2 and CH_3CO), 3.9–

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(12) Since Sowa[13] has recently reported that the use of 10 parts of acetic acid to 1 of acetic anhydride for the acetolysis of ribose caused epimerization to arabinose, we prepared **6** using a 1:1 mixture which was shown *not* to cause epimerization.

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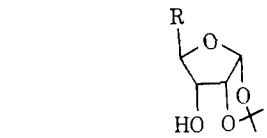
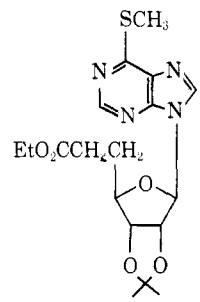
4.4 (m, 3, H_4 and CH_3CH_2O), 4.8–5.4 (m, 2, H_2, H_3), 6.09 (s, br, H_1 of β anomer), 6.35 (d, br, H_1 of α anomer) (1:3:α:β).[14,15] On tlc this mixture traveled as two closely spaced spots both of which gave, after deacetylation with ammonia, a positive metaperiodate Schiff's test.[16]

Fusion of **6** (3.9 g, 11.2 mmol) with 2,6-dichloropurine (2.1 g, 11 mmol) and 100 mg of *p*-toluenesulfonic acid at 140° gave 4.8 g of a mixture of **6** with not two, but *four* nucleosides, all of which were shown to be 9-glycosyl-2,6-dichloropurines by conversion to the 2-chloro-6-dimethylaminopurine nucleosides (λ_{max} in nm: pH 1, 243 (sh), 274; pH 7, 253 (sh), 275).[17–19]

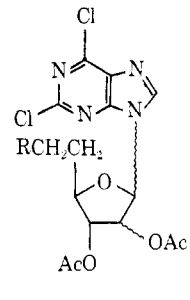
The 2,6-dichloropurine nucleosides (2.56 g, 47%), separated and obtained pure by a combination of preparative tlc and column chromatography on silica gel using benzene–ether as the eluent, were characterized by their chromatographic travel, their reaction (after deacetylation with ammonia) to the metaperiodate Schiff's test,[16] and their uv, ir, pmr, and mass spectra. Two of the nucleosides (A and B) gave a metaperiodate Schiff's test typical of ribonucleosides, whereas the other pair (C and D) gave a much slower developing color typical of arabinosides and distinctly different from xylosides.[20] All four nucleosides gave similar mass spectra with the correct molecular ion at *m/e* 474, the purine base ion at *m/e* 187, and the sugar ion at *m/e* 287. The ultraviolet spectra of the four were essentially identical with maxima at 273 nm at pH 1 and 7.[17] The ir spectra of all four nucleosides were remarkably similar except for the 1300–1000-cm^{-1} region. The bands due to sugar C–O vibrations in this region were quite similar for A and B, but those of C and D were distinctly different from those of A and B and quite similar to each other, indicating that the four nucleosides were probably two anomeric pairs. The identities of these isomeric nucleosides were firmly established by their pmr spectra: compound A, δ 1.23 (t, 3, CH_3CH_2O), 2.07 and 2.13 (s, 6, CH_3CO), 1.7–2.8 (m, 4, CH_2CH_2), 3.9–4.6 (m, 3, CH_3CH_2O and $H_{4'}$), 5.44 and 5.82 (m, 2, $H_{2'}$, $H_{3'}$), 6.12 (d, $J_{1',2'}$ = 5 Hz, 1, $H_{1'}$), and 8.25 (s, 1, H_8); compound B, 1.26 (t, 3, CH_3CH_2O), 1.87 and 2.41 (s, 6, CH_3CO), 1.8–2.4 (m, 4, CH_2CH_2), 4.17 (q, 2, CH_3CH_2O), 4.3–4.8 (m, 1, $H_{4'}$), 5.35 and 5.76 (m, 2, $H_{2'}$, $H_{3'}$), 6.61 (d, $J_{1',2'}$ = 5.4 Hz, 1, $H_{1'}$), and 8.36 (s, 1, H_8). These spectra were very similar to those of ethyl 1,5,6-trideoxy-2,3-*O*-isopropylidene-1-[6-(methylthio)purin-9-yl]-β-D-*ribo*-heptofuranuronate (**7**)[21] and 9-(2,3,6-tri-*O*-acetyl-5-deoxy-β-D-*ribo*-hexofuranosyl)-2,6-dichloropurine (β-*ribo*-**8**).[22] Although the coupling constant of the anomeric proton of these furanosylpurines could not be used to establish the configuration at the glycosyl center, there appears to be no exception to the empirical observations that the signal from the anomeric proton of cis nucleosides occurs at lower field than that of trans nucleosides.[8] On this basis, and by a comparison of the position of this band in the spectrum of A with its position in the spectra of **7** (6.10) and **8** (6.12), the structure of the first nucleoside can be assigned as β-ribofuranose (β-*ribo*-**9**) and the second nucleoside as α-ribofuranose (α-*ribo*-**9**).



3, R = CHO
4, R = CH=CHCO$_2$Et
5, R = (CH$_2$)$_2$CO$_2$Et



7



8, R = CH_3CO_2
9, R = EtO_2C

The pmr spectra of C and D showed that a change had occurred in the sugar moiety. In particular, the small values of $J_{2',3'}$ (~2.5 Hz in C and ~2 Hz in D) indicated that $H_{2'}$ and $H_{3'}$ were on opposite sides of the ring. In order to determine whether epimerization had occurred at $C_{2'}$ or $C_{3'}$, all assignments were checked by indor experiments, and the 5′-CH_2 peaks were located by the same technique. Subsequent integration of $H_{3'}$ while irradiating the 5′-CH_2 peaks indicated a sufficient enhancement in intensity (16% for C, 24% for D) due to the nuclear Overhauser effect to show that $H_{3'}$ is on the same side of the ring as the 5′-CH_2. At the same time no enhancement, within the accuracy of the instrument, in intensity of the $H_{2'}$ peak was observed. Thus, the sugar moieties of C and D were shown to be arabinose rather than xylose. C was assigned as the α anomer (α-*arabino*-**9**) on the basis of the chemical shift of $H_{1'}$ (upfield from $H_{1'}$ of D, which must then be β-*arabino*-**9**) and the small value of $J_{1',2'}$ (~2.5 Hz).[14] Compound C showed the following pmr spectral data: δ 1.25 (t, 3, CH_3CH_2O), 2.11 and 2.18 (s, 6, CH_3CO), 1.8–2.6 (m, 4, CH_2CH_2), 4.16 (q, 2, CH_3CH_2O), 4.53 (m, 1, $H_{4'}$), 5.20 (m, 1, $H_{3'}$), 5.73 (m, 1, $H_{2'}$), 6.23 (d, 1, $H_{1'}$), and 8.28 (s, 1, H_8); compound D, 1.25 (t, 3, CH_3CH_2O), 1.95 and 2.18 (s, 6, CH_3CO), 2.0–2.7 (m, 4, CH_2CH_2), 4.0–4.3 (m, 3, CH_3CH_2 and $H_{2'}$), 5.21 (m, 1, $H_{3'}$), 5.43 (m, 1, $H_{2'}$), 6.53 (d, $J_{1',2'}$ = 4.2 Hz, 1, $H_{1'}$), and 8.31 (s, 1, H_8).

Thus, the fusion reaction gave two anomeric pairs: a 30% yield of the ribonucleosides **9** (3β:1α) and a 17% yield of the arabinonucleosides **9** (3α:1β). Formation of the arabinonucleosides could only have occurred by

(14) Spectra were obtained on 5–10% solutions in $CDCl_3$ with tetramethylsilane as internal reference, with the Varian A-60A and XL-100-15 spectrometers. Chemical shifts reported for multiplets are the approximate centers.

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epimerization of the original ribofuranose **6** during the acidic fusion reaction since the identity and purity of **6** were established prior to the fusion reaction. The fusion reaction has been applied to the preparation of many purine and pyrimidine nucleosides[23,24]—mostly nucleosides from 1,2,3,5-tetra-*O*-acetyl-D-ribofuranose—and epimerization has not been observed heretofore. Whether the unique structure of this sugar is responsible for epimerization in this case is not known,[25] but the most logical mechanism by which it might occur would be migration of the 1-acetoxy group of β-**6** to C-2 *via* an ortho ester–ion intermediate. In any event, the occurrence of epimerization in this widely used reaction makes conclusive proof of the structure of nucleosides prepared in this manner vital.

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Activated Metals. I. Preparation of Highly Reactive Magnesium Metal

Sir:

We would like to report a new method for preparing magnesium metal in a very reactive state. Previous to our studies, there were three modifications of the general procedure for the direct synthesis of difficultly formed Grignard reagents from the reaction of magnesium metal and an organic halide: (1) use of higher reaction temperatures, (2) use of a more strongly coordinating solvent,[1-5] and (3) activation of the magnesium metal.[6-10] The third method consists of activation of the magnesium by reduction of the size of the metal particle[9] or by a chemical reaction. The Gilman catalyst,[6] which involves the addition of iodine to activate the magnesium, is representative of this technique. Ethylene bromide or ethyl bromide has been employed in catalytic amounts to activate the magnesium surface and in molar quantities as an entrainer.[7] Use of certain transition metal halides has proven them to be useful catalysts.[8] Recently, Ashby combined the three techniques to prepare some alkylmagnesium fluorides.[10]

Our new process produces magnesium in a finely divided state and free of any metal oxides. The reactivity of this metal is vastly superior to that of any of the methods described above. For example, we have prepared phenylmagnesium bromide from phenyl bromide and our activated magnesium in THF at −78°. In only 30 min over a 60% yield was realized. The per cent yield of the Grignard reagent was based on the amount of benzoic acid produced upon treatment with carbon dioxide. Treatment of chlorobenzene with normal magnesium at room temperature for 90 min gave no phenylmagnesium chloride. In contrast, treatment of chlorobenzene with our activated magnesium at room temperature for 90 min yielded 62% of phenylmagnesium chloride. Reaction with phenyl bromide at room temperature is very exothermic and very rapid. Within 2–3 min yields of over 65% phenylmagnesium bromide were realized. Further evidence of the high reactivity of the metal comes from the reaction of fluorobenzene with the activated metal. Until this report, all efforts to prepare phenylmagnesium fluoride from fluorobenzene and magnesium had failed.[10] These attempts included use of all the modifications listed at the beginning of this paper and in some cases involved reflux times of several days. Refluxing fluorobenzene and our activated metal in diglyme for only 1 hr yielded over 5% benzoic acid after treatment with carbon dioxide.[11]

The general process for generating the finely divided metal involves the reduction of anhydrous magnesium chloride or anhydrous magnesium bromide[12] in an inert ethereal solvent under an inert atmosphere. The reduction can most conveniently be carried out by using an alkali metal and an ethereal solvent whose boiling point exceeds the melting point of the alkali metal. The metal salt to be reduced should be at least partially soluble in the ethereal solvent chosen. Solvent combinations that we have found useful are potassium–THF and diglyme–sodium.[13] The reaction time for reduction varies from 1 to 2 hr for the THF–K–MgX_2 combination to 5–6 hr for the diglyme–Na–MgX_2 combination. The reduction yields a fine black powder of magnesium metal which can be immediately used to prepare the Grignard reagent. In most cases, the Grignard reagents were prepared by simply adding the alkyl or aryl halide directly to the suspension of powdered magnesium metal. No attempt was made to remove the sodium or potassium salts formed in the reductions. We have removed the original solvent from the powdered metal in some cases either by vacuum or decanting. This metal powder gave similar results to that described above. Any problem with unreacted alkali metals can be avoided by starting with an excess of magnesium halide.

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(11) Use of transition metal halides as catalysts, higher reflux temperatures, and longer reaction times are being currently investigated.
(12) The chloride has the advantage of being commercially available whereas the magnesium bromide must be prepared from magnesium and ethylene bromide.
(13) At this point, we have not tried dimethoxyethane but we are certain it will work also. Dioxane did not work.