The two higher energy processes, both of which have barriers of 9.2 kcal/mol, lead to exchange of all sites. These two processes correspond to an *ESS* mechanism and a topomerization, in which only one of the *tert*-butyl groups undergoes permutational rearrangement (L. D. Iroff, unpublished results).

(20) For the preparation of **2**, see Lee, H.-H. Ph.D. Thesis, University of Michigan, Ann Arbor, Mich., 1971.

(21) Previously, Bartell and Bürgi[22] had estimated an activation energy of 16 kcal/mol for the enantiomerization of **2**, by use of force-field calculations in which all three *tert*-butyl groups were driven in synchrony so as to maintain C_3 symmetry throughout;[23] "whether a reaction coordinate of lower symmetry exists that corresponds to a lower activation energy was not investigated."[22]

(22) Bartell, L. S.; Bürgi, H. B. *J. Am. Chem. Soc.* **1972**, *94*, 5239.

(23) This approach was necessitated by limitations in the dimensions of the computer program used (Bürgi, H. B., private communication).

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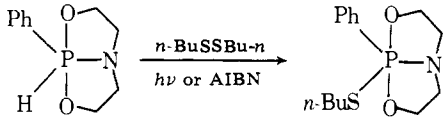
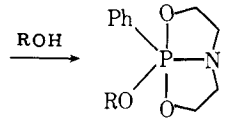
Free-Radical Alkylthiylation of a Pentacovalent P-H Compound

Sir:

The preparation of new pentacovalent phosphorus derivatives (phosphoranes) remains a synthetic challenge, even though molecules of increasingly complex structure have lately been prepared.[1] Among these are various pentacovalent P-H compounds. A recent review[2] tabulated well over 100 such molecules, including a very large fraction of bicyclic and spiro compounds. We report here the radical-initiated conversion of the bicyclic P-H compound **1**[3] to the corresponding PSR derivative **2** in high yields. This represents a hitherto un-



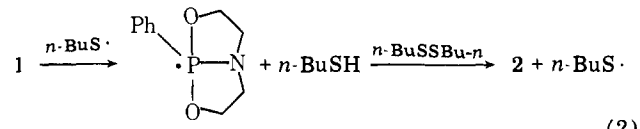
1 **2**



(1)

3, RO = *n*-PrOH
4, RO = EtOH

discovered free-radical chain reaction of such materials, which almost certainly proceeds via the phosphoranyl radical intermediate **5**. Furthermore, the structurally novel phosphorane **2** is not otherwise synthetically accessible. Such a substitution reaction, if general, holds potential promise for the functionalization of the many synthetically available pentacovalent P-H precursors[2] as their PSR derivatives.



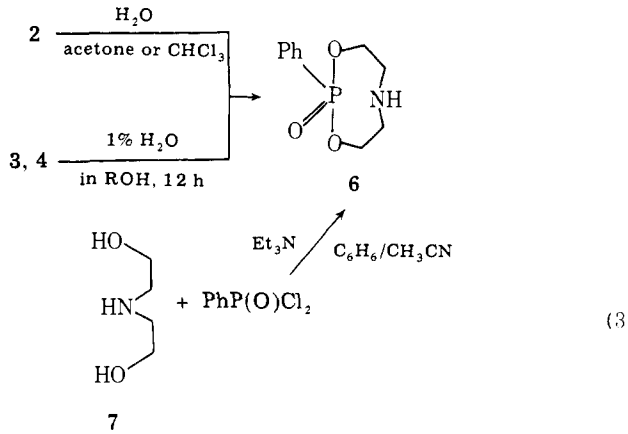
5 (2)

No reaction occurred when **1** and *n*-BuSSBu-*n* were allowed to stand 1 day in the dark at room temperature or overnight at 65 °C. However, when a benzene solution, 0.2 M in both **1** and *n*-BuSSBu-*n*, was irradiated through Pyrex with a medium-pressure 450-W Hanovia mercury lamp, **1** was completely consumed in 30 min in a very clean reaction which gave **2** in 70–80% yield (GLC, hexadecane as internal standard). A completely analogous reaction was initiated thermally at 65 °C by a trace of azobisisobutyronitrile. *n*-Butyl mercaptan was identified in the reaction mixtures but not measured quantitatively.

Pure **2** (>99%) could be isolated by rapid repeated short-column filtration chromatographies on silica gel: ^{31}P NMR δ −29.5[4] (C_6D_6); ^{1}H NMR δ (C_6D_6) 0.78 (3 H, distorted t, J_{HH} = 6 Hz, $CH_3CH_2CH_2CH_2S$), 1.10–1.74 (4 H, m, $CH_3CH_2CH_2CH_2S$), 2.56–2.92 (6 H, m, NCH_2 and $CH_3CH_2CH_2CH_2S$), 3.36–3.90 (4 H, m, OCH_2), 7.13–7.36 (3 H, m, *m*,*p*-C_6H_5), 7.90–8.23 (2 H, m, *o*-C_6H_5P); MS, *m/e* 300 (M^+, 0.7), 210 (M^+ − *n*-BuS, 100); high-resolution MS, *m/e* 210.0676, calcd 210.0684 ($C_{14}H_{23}N_2O_2PS$).

On treatment with a sixfold excess of *n*-PrOH, phosphorane **2** (~0.04 M in C_6H_6) was slowly converted to the alkoxy derivative **3**[5] (δ ^{31}P, −39.4, C_6D_6) in 16 h at room temperature in 65% yield (GLC) at 35% consumption of **2**. Similarly, from reaction with EtOH, derivative **4**[5] (δ ^{31}P, −39.4, C_6D_6) resulted in 72% yield at 65% conversion.

Phosphorane **2** was readily hydrolyzed in a few days in H_2O-saturated $CHCl_3$ or in 10 h in 2% H_2O–acetone at room temperature to the eight-membered ring phosphonate **6** (eq 3). Phosphonate **6** was also formed on hydrolysis of **3** and **4**



(3)

(~70% yields) and on reaction of amino alcohol **7** with $PhP(O)Cl_2$ (70% isolated yield): mp of **6** 57–58 °C (ligroin); high-resolution MS 227.0745, calcd 227.0712 ($C_{10}H_{14}NO_3P$); ^{1}H NMR ($CDCl_3$) δ 2.85 (2 H, d of d of d, CH_2NHCH_2) 3.22 (2 H, d of d of d, CH_2NHCH_2), 3.85–4.62 (4 H, m, OCH_2), 7.53 (3 H, m, C_6H_5P), 7.87 (2 H, m, C_6H_5P), 1.87 (1 H, s, NH).

Although phosphoranyl radicals have been generated previously by alkoxy-radical attack on pentacovalent P-H compounds,[6] the ability of a free radical so unreactive as RS· to abstract hydrogen (reaction 2) suggests that the P-H bond is very weak indeed. Nonetheless, the resulting phosphoranyl radical **5**[7] is sufficiently reactive that attack on disulfide sulfur occurs efficiently even at *n*-BuSSBu-*n* concentrations of 0.2 M and less, and a free-radical chain reaction ensues. The conversion **5** → **2** is the first example of such a displacement process involving a phosphoranyl radical. Whether its efficiency is the result of the known[9] high stability of pentacovalent phosphorus at the bridgehead position of the [3.3.0]bicyclooctane ring system remains speculative. Certain phosphoranyl radicals have earlier been shown to be intercepted by reaction[10] with O_2, by additions to olefinic double bonds,[6,11] and by spin trapping with *t*-BuNO[6] and 5,5-dimethyl-1-pyrroline 1-oxide.[12] Phosphoranyl radicals in which phosphorus is part of a five-membered ring are generally stabilized with respect to α and β scission processes.[6,13] The above thiylalkylation process therefore should be quite generally applicable to the many known spiro and bicyclic pentacovalent P-H compounds.[2,14]

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References and Notes

(1) A review of the many known X-ray structures of phosphoranes was published recently: W. S. Sheldrick, *Top. Current Chem.*, **73**, 1 (1978). For some examples of recently reported structurally novel phosphoranes, see: B. C. Campbell, D. B. Denney, D. Z. Denney, and L. S. Shih, *J. Chem. Soc., Chem. Commun.*, 854 (1978); A. Schmidpeter and J. H. Weinmaier, *Angew. Chem., Int. Ed. Engl.*, **16**, 865 (1977); I. Granoth and J. C. Martin, *J. Am. Chem. Soc.*, **100**, 7434 (1978); F. Ramirez, M. Nowakowski, and J. F. Maracek, *ibid.*, **98**, 4330 (1976); **99**, 4515 (1977); B. C. Burros, N. J. De'Ath, D. B. Denney, D. Z. Denney, and I. J. Kipnis, *J. Am. Chem. Soc.*, **100**, 7300 (1978); A. C. Sau and R. R. Holmes, *J. Organomet. Chem.*, **156**, 253 (1978); J. E. Richman, *Tetrahedron Lett.*, 559 (1977); J. E. Richman and T. J. Atkins, *ibid.*, 4333 (1978).

(2) J. F. Brazier, D. Houalla, M. Koenig, and R. Wolf, *Top. Phosphorus Chem.*, **8**, 99 (1976).

(3) D. Houalla, T. Mouheich, M. Sanchez, and R. Wolf, *Phosphorus*, **5**, 229 (1975).

(4) Negative ^{31}P chemical shifts are upfield from 85% H_3PO_4 as external standard.

(5) Phosphoranes **3** and **4** were prepared independently by photoreaction of **1** with EtOOEt and *i*-PrOOPr-*i* and purified by column chromatography (T. Kawashima, unpublished results). This study will be reported separately.

(6) D. Griller and B. P. Roberts, *J. Chem. Soc., Perkin Trans. 2*, 1416 (1973).

(7) Since this manuscript was submitted, ESR evidence showing that **5** is indeed a phosphorus-centered radical rather than one[8] with the odd electron located on the ring has been published: J. H. H. Hamerlinck, P. Schipper, and H. M. Buck, *J. Chem. Soc., Chem. Commun.*, 350 (1979).

(8) A. G. Davies, M. J. Parrott, and B. P. Roberts, *J. Chem. Soc., Chem. Commun.*, 973 (1974).

(9) A. Schmidpeter, J. H. Weinmaier, and E. Glaser, *Angew. Chem., Int. Ed. Engl.*, **16**, 549 (1977); A. Schmidpeter and J. H. Weinmaier, *ibid.*, **14**, 489 (1975).

(10) J. A. Howard and J. C. Tait, *Can. J. Chem.*, **56**, 2163 (1978).

(11) A. G. Davies, M. J. Parrott, and B. P. Roberts, *J. Chem. Soc., Perkin Trans. 2*, 1066 (1976).

(12) P. Tordo, M. Boyer, A. Friedmann, O. Santero, and L. Pujol, *J. Phys. Chem.*, **82**, 1742 (1978); radical **5** was among those trapped in this manner.

(13) J. W. Cooper, M. J. Parrott, and B. P. Roberts, *J. Chem. Soc., Perkin Trans. 2*, 730 (1977).

(14) NOTE ADDED IN PROOF. The generality of the reaction is supported by the finding that the tetracyclic aminophosphorane reported by J. E. Richman and T. H. Atkins, *Tetrahedron Lett.*, 4333 (1978), undergoes a parallel reaction with MeSSMe (private communication from J. E. Richman).

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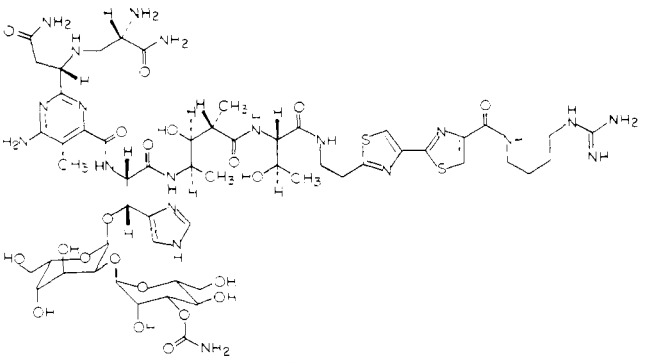
Synthesis of L-*erythro*-β-Hydroxyhistidine from D-Glucosamine

Sir:

Bleomycin is the generic name for a family of structurally related antitumor antibiotics elaborated by *Streptomyces verticillus;* the compounds are of current interest because of their clinically useful activity against squamous cell carcinomas and malignant lymphomas, including Hodgkin's disease.[1] As part of an effort to effect the total synthesis of bleomycin B_2 (**1**),[2] we have investigated methods suitable for the preparation of L-*erythro*-β-hydroxyhistidine,[3] a novel amino acid constituent of the glycopeptide-derived antibiotic.

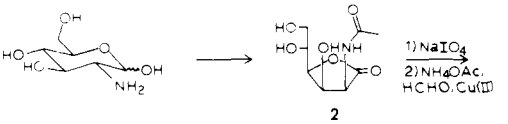
β-Hydroxyhistidine has been prepared previously by Takita et al.,[4] who obtained it in unspecified yield as a 2.5:1 mixture of the racemic erythro and threo species by treatment of imidazole-4-carboxaldehyde[5] with copper glycinate in sodium carbonate solution.[6] We found that substitution of *N*-pyruvylideneglycinatoaquocopper(II) dihydrate resulted in better (70–80%) yields of DL-*erythro*-β-hydroxyhistidine,[7] which could be resolved via the agency of D-amino acid oxidase. The



1

product had $[\alpha]^{25}_D$ +35° (*c* 1.34, H_2O), lit.[4] $[\alpha]^{28}_D$ +40° (*c* 1, H_2O). Although this improved procedure provided a workable route to L-*erythro*-β-hydroxyhistidine, a more efficient, stereospecific synthesis was sought.

2-Acetamido-2-deoxy-D-mannono-1,4-lactone (**2**) is a masked amino acid readily accessible from D-glucosamine.[9] Although lactones of this type undergo facile solvolysis,[11] it was possible to effect selective oxidative cleavage of the C-5–C-6 bond with aqueous $NaIO_4$ (1.0 equiv, 4 °C, 50 min) to afford the desired C-5 aldehyde, convertible directly to **3** after



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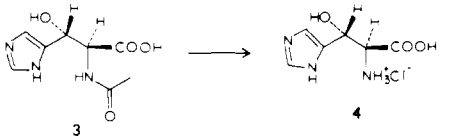
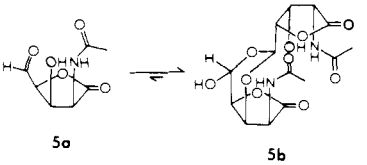


3 4

removal of $NaIO_3$ or isolable in quantitative yield as a white solid, mp 148–150 °C dec. In analogy with the work of Schaffer and Isbell[12a] and Inch[12b] on the structure of the species resulting from oxidation of 1,2-*O*-isopropylidene-α-D-glucofuranose, this solid was assigned structure **5b.** Consistent with its formulation as a (reversibly formed) hemiacetal dimer, the mass spectrum of **5** included a fragment ion at *m/e*



5a 5b

338 ($M^+ - 2H_2O$); the IR spectrum (KBr) had only a weak absorption at 2930 cm^{-1} corresponding to an aldehyde group, and the NMR (Me_2SO-d_6, Me_4Si) had a correspondingly small signal at δ 9.52 (10% of the integration that would have been expected for **5a**), as well as two sets of doublets of unequal intensity centered at δ 8.17 and 8.26 (NH, J = 9 Hz).[10] As anticipated, though, **5** could also be converted (65% yield) to the respective 2,4-dinitrophenylhydrazone, which was characterized fully.[13]

Conceptually, the conversion **5** → **3** involves simple solvolysis of the 1,4-lactone and construction of an imidazole utilizing C-4 and C-5 of the carbohydrate. In practice, however, these transformations proved somewhat more difficult to effect, since both are ordinarily carried out in the presence of strong bases and imidazole formation proceeds only at elevated temperature in the presence of Cu(II);[14] unfortunately both **3** and **5** decompose readily under these conditions. To maximize the production of **3**, and minimize its subsequent de-

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