yield of hexafluoroacetone. Perfluoroisobutylene oxide requires 320° for 24 hr for significant formation of hexafluoroacetone and difluorocarbene, suggesting that the displacement of difluorocarbene from carbonyl fluoride by bis(trifluoromethyl)carbene at 180° occurs by way of excited perfluoroisobutylene oxide.

Difluorocarbene reacts with OPF_3 in two ways: as a reducing agent and as a fluorinating agent (eq 1 and 2). These reactions are isokinetic at 60° At

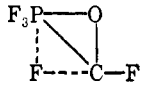
$$CF_2 + OPF_3 \longrightarrow OCF_2 + PF_3 \quad (1)$$

$$CF_2 + OPF_3 \longrightarrow CO + PF_5 \quad (2)$$

100°, reaction 1 accounts for 95% of the products and reaction 2 for 5%. At 25°, reaction 1 accounts for 5% and reaction 2 for 95%.[8] From the product ratios we estimate that reaction 1 has an enthalpy and entropy of activation 18 kcal mole^{-1} and 50 eu, respectively, greater than those of reaction 2. By analogy to the carbene–ketone adduct[6] we suggest that addition of CF_2 to the PO bond is the first step common to reactions 1 and 2. Reaction 1 then pro-

$$CF_2 + F_3PO \longrightarrow F_3P\overset{O}{\diagdown\diagup}CF_2$$

ceeds by breaking the PO bond, or the PC bond, or both. Reaction 2 proceeds by way of a fluorine shift from C to P *via* a very tight bicyclic transition state to



give $F_4PC(=O)F$ (not isolable at 25°) which shifts fluorine once more to give CO and PF_5.

Bis(trifluoromethyl)carbene (from bis(trifluoromethyl)diazomethane) reacts with OPF_3 at 160° or in sunlight at 25° to give hexafluoroacetone.

We are applying the reduction of OPF_3 as a probe for carbenes in more complex systems. For example, pentafluoroethyltetrafluorophosphorane, $CF_3CF_2PF_4$, decomposes at 240° in platinum with a half-life of 12 hr to give tetrafluoroethylene and pentafluorophosphorane. Trifluoromethylfluorocarbene is revealed as an intermediate because trifluoroacetyl fluoride is obtained in 80% yield with a threefold excess of OPF_3.

$$CF_3CF_2PF_4 \longrightarrow CF_3CF + PF_5$$

$$CF_3CF \longrightarrow F_2C{=}CF_2$$

$$OPF_3 + CF_3CF \longrightarrow PF_3 + CF_3\overset{O}{\overset{\|}{C}}F$$

Similarly, *n*-perfluoropropyltetrafluorophosphorane decomposes at 240° predominantly *via* an α-fluorine shift.

and hexafluoroacetone has been demonstrated by Moore.[7] The boiling point is 2°; infrared absorption is at 1500, 1335, 1280, 1255, 1225, 1090, 1025, 985, 725, 718, and 712 cm^{-1}. ^{19}F nmr resonances are at 72 ppm for CF_3 and 112 ppm for CF_2 from $FCCl_3$.

(7) Reported by D. P. Carlson and A. S. Milian, Fourth International Symposium on Fluorine Chemistry, Estes Park, Colo., 1967.

(8) The 25° source of CF_2 used was $(CF_3)_2PF_3 \rightarrow CF_2 + CF_3PF_4$ (half-life 3 days). $(CF_3)_3PF_2 \rightarrow 3CF_2 + PF_5$ served for the experiments at 60° (half-life 6 months) and 100° (half-life 12 hr). Experiments were run in sealed-glass or platinum tubes for at least two half-lives. The product ratios are independent of pressure. Reaction 1 was also observed using perfluorocyclopropane as CF_2 source[9] at 220° or perfluoro(methylcyclopropane) at 190°. The latter extrudes CF_2 exclusively, with no indication of CF_3CF.

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Walter Mahler

Contribution No. 1362, Central Research Department Experimental Station, E. I. du Pont de Nemours and Co. Wilmington, Delaware 19898

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Pyrrolo[2,3-*d*]pyrimidine Nucleoside Antibiotics. Total Synthesis and Structure of Toyocamycin, Unamycin B, Vengicide, Antibiotic E-212, and Sangivamycin (BA-90912)[1]

Sir:

The antibiotic toyocamycin was first isolated from *Streptomyces toyocaensis* by Nishimura and coworkers[2] and later by Ohkuma[3] from *Streptomyces* strain 1922. Recently antibiotic 1037[4] has been shown[5] to be identical with toyocamycin. The unusual biological properties of toyocamycin[2,3] and its antitumor activity[6,7] have stimulated considerable interest in this antibiotic. Preliminary degradation studies[3,8] resulted in a tentative structure assignment for toyocamycin as 4-amino-5-cyano-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine. Sangivamycin has been isolated from an unidentified species of *Streptomyces*[9] and was at that time referred to as BA-90912. Sangivamycin was reported to possess cytotoxicity against HeLa cells grown in cell cultures and to exhibit significant activity against Leukemia 1210 in mice. Sangivamycin has produced no evidence of toxicity in humans at maximally tolerated doses and is presently undergoing human clinical trial against leukemia.[10] It has been noted[11] that sangivamycin is structurally similar to toyocamycin. However, a recent review[12] points to the fact that the actual site of glycosidation, anomeric configuration, and structure of the sugar moiety for sangivamycin and toyocamycin have not been unequivocally established.

We now wish to report a total synthesis of toyocamycin (VIa) and sangivamycin (VIb) and the unequivocal assignment of their structures.

Ring closure of 2-amino-5-bromo-3,4-dicyanopyrrole[13] with formamidine acetate in 2-ethoxyethanol at reflux temperature furnished a 65% yield of 4-amino-6-bromo-5-cyanopyrrolo[2,3-*d*]pyrimidine (I): mp 300°, λ_{max}^{EtOH} 284 (ε 13,800) and 250 mμ (ε 7800). A mixture of I, acetic anhydride, and xylene was heated at reflux temperature for 18 hr to afford the monoacetylated product, 4-acetamido-6-bromo-5-cyanopyrrolo[2,3-*d*]pyrimidine (II, 94%), mp 265° dec.

A mixture of II and 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose was heated at 175° in the presence of a catalytic amount of bis(*p*-nitrophenyl) phosphate[14] for

(1) This work was supported in part by Research Contract No. PH 43-65-1041, Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service.

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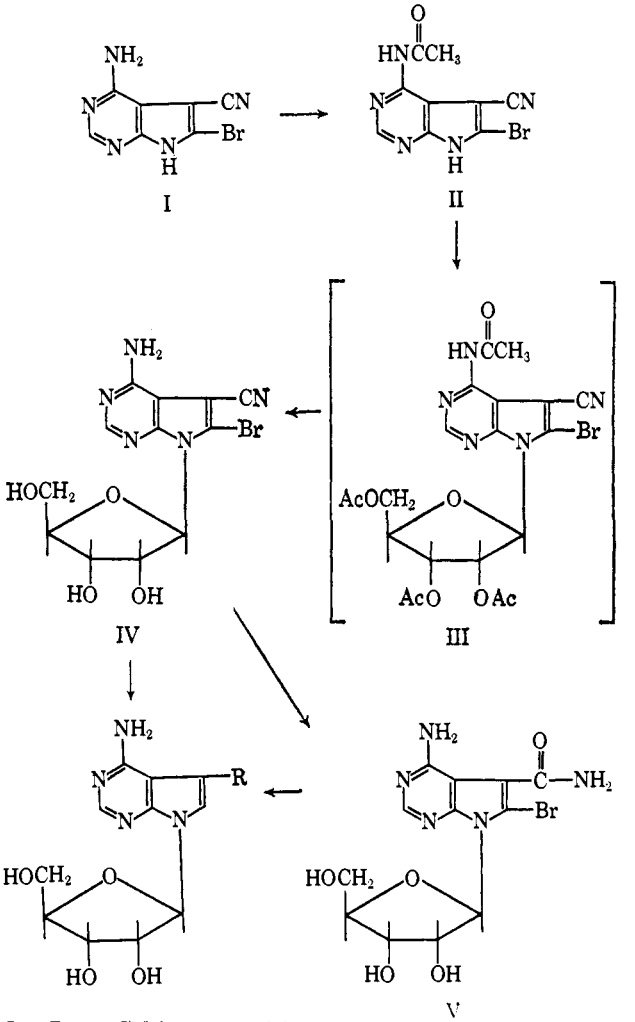
(14) T. Hashizume and H. Iwamura, *Tetrahedron Letters*, 3095 (1965).

25 min. This reaction mixture was then applied to a column of Woelm neutral alumina and eluted with mixtures of petroleum ether–chloroform. Preparative layer chromatography was then utilized to furnish the acetylated nucleoside III as a pale yellow syrup. Complete deacetylation of III was accomplished with methanolic ammonia at room temperature to furnish a 92% yield of 4-amino-6-bromo-5-cyano-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (IV): mp 245–247° dec; λ_{max}^{EtOH} 284 mμ (ε 18,300). Recent studies in this laboratory have shown that ribosidation or alkylation[15] of 6-substituted 4-amino-5-cyanopyrrolo[2,3-*d*]-pyrimidines in the pyrimidine ring produces a 15–30-mμ bathochromic shift while alkylation in the pyrrole ring produces only a small hypsochromic shift if any shift is observed at all. The ultraviolet absorption maxima recorded in ethanol for I and the nucleoside derivative IV are identical. Thus, the D-ribofuranosyl moiety was assigned to the pyrrole ring at N-7.

Removal of the 6-bromo group of IV with 5% palladium on powdered charcoal in a hydrogen atmosphere afforded an 88% yield of 4-amino-5-cyano-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (VIa, toyocamycin): mp 243°; λ_{max}^{EtOH} 288 (shoulder) (ε 9800), 278 (ε 5100), and 231 mμ (ε 9300); infrared absorption band at 2230 cm^{-1} (CN); $[\alpha]^{26}D$ −55.6 ± 1.3° (*c* 1.0, 0.1 *N* HCl).[16] A mixture melting point of the above product and toyocamycin[17] showed no depression. The ultraviolet, infrared, and pmr spectra of VIa and toyocamycin were superimposable. The chromatographic mobilities of VIa in four solvent systems were identical with those observed for natural toyocamycin.[17] The 2′,3′-*O*-isopropylidene-5′-*O*-tosyl derivative of toyocamycin was prepared by standard procedures and warm dimethyl sulfoxide-d_6 effected intramolecular quaternization to yield 2′,3′-*O*-isopropylidene-5′-N_1-toyocamycin cyclonucleoside. The appearance in the pmr of a sharp singlet at δ 6.65 (1 H) was assigned to the anomeric proton which established[18] the β configuration for all nucleosides here reported. Thus the site of ribosidation, anomeric configuration, and structure of the carbohydrate moiety for toyocamycin have been confirmed and the structure for toyocamycin established as 4-amino-5-cyano-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (VIa).

Unamycin B isolated from a culture of *Streptomyces fungicidicus*[19,20] and antibiotic E-212 isolated[21] from *Streptomyces* sp. E-212 have been described as related to toyocamycin.[19,21] Authentic samples[22,23] of unamycin B and antibiotic E-212 were rigorously compared with toyocamycin in our laboratory, which proved that these antibiotics were identical with toyocamycin. Vengicide has been isolated from *Streptomyces vendargensis*[24,25] and since a number of physical properties of this antibiotic were similar to those of toyocamycin, a sample was obtained for comparison.[26] Vengicide was found in our laboratory also to be identical with toyocamycin.

The total synthesis and complete structural assignment of sangivamycin (VIb) has also been achieved. Treatment of IV with 30% hydrogen peroxide in concentrated ammonium hydroxide solution at room temperature furnished a crystalline product in 65% yield, mp 221°. This nucleoside was assigned the structure 4-amino-6-bromo-5-carboxamido-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (V) on the basis of elemental analysis[16] and pmr spectra. Removal of the 6-bromo group from V with 5% palladium on powdered charcoal in a hydrogen atmosphere pro-



VIa, R = –CN (toyocamycin)
b, R = –C(=O)–NH$_2$ (sangivamycin)
c, R = –C(=O)–OH
d, R = –H (tubercidin)

(15) R. L. Tolman, R. K. Robins, and L. B. Townsend, *J. Heterocyclic Chem.*, **4**, 230 (1967).
(16) Satisfactory elemental analyses were obtained for all new compounds reported. Optical rotation of an authentic sample of toyocamycin under similar conditions was $[\alpha]^{27}D$ −55.7 ± 0.9°.
(17) The authors wish to thank Dr. Haruo Nishimura, Shionogi and Co. Ltd. Osaka, and Dr. Kazuhiko Ohkuma, Institute of Physical and Chemical Research, Tokyo, for authentic samples of toyocamyin.
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(23) The authors wish to thank Dr. Mitsuo Rikimaru of the Tohoku University School of Medicine, Sendai, Japan, for an authentic sample of antibiotic E-212.
(24) A. P. Struyk and A. A. Stheeman, *Chem. Abstr.*, **51**, 10009*a* (1957); British Patent 764,198.
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(26) The authors wish to thank Dr. J. C. Hoogerheide, Koninklijke, Nederlandsche Gist-en Spiritusfabriek, Delft, The Netherlands, for a sample of vengicide.

ceeded smoothly to afford 4-amino-5-carboxamido-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (VIb) in 83% yield: mp 260°, λ_{max}^{EtOH} 278 (ε 15,100) and 229 mμ (ε 8200); $[\alpha]^{26}D$ −45.7 ± 1.9° (*c* 1.0, 0.1 *N* HCl).[27] A comparison of chromatographic mobilities, ultraviolet absorption, and infrared spectra of VIb with those of an authentic sample of sangivamycin[27] established that the samples were identical. Additional evidence for the structural assignment of sangivamycin and toyocamycin was furnished by the conversion of sangivamycic acid to the related pyrrolo[2,3-*d*]pyrimidine antibiotic tubercidin since the structure of tubercidin has previously been unequivocally established.[28] Sangivamycic acid (VIc) has been previously prepared[8] as an intermediate but was never characterized. Sangivamycic acid hydrochloride was prepared in our laboratory by heating toyocamycin at reflux temperature in 3 *N* hydrochloric acid in a nitrogen atmosphere for 12 hr to obtain a 55% yield of VIc: mp 238° dec; λ_{max}^{EtOH} 279 (ε 13,500) and 231 mμ (ε 7600). Decarboxylation was accomplished by immersion of VIc in a preheated oil bath (238°) for approximately 10 sec; this gave a dark amber melt. An aqueous ethanol extract of this melt furnished tubercidin (VId, 4-amino-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine) in 13% yield. The identity of VId was confirmed by rigorous comparison with authentic tubercidin.[29]

(27) The authors wish to thank Dr. K. V. Rao for an authentic sample of sangivamycin hydrochloride which showed an optical rotation of $[\alpha]^{26}D$ −42.2 ± 1.9° under similar conditions.

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(30) National Aeronautics and Space Administration Fellow, 1965–1967.

Richard L. Tolman,[30] Roland K. Robins
Leroy B. Townsend
Department of Chemistry, University of Utah
Salt Lake City, Utah 84112
Received September 21, 1967

The Rearrangement of N,N′-Dimethylhydrazobenzene[1]

Sir:

Although the benzidine rearrangement has been the subject of many investigations,[2] its intimate mechanism continues to be the subject of considerable discussion and disagreement, with some[3] preferring a concerted mechanism in which the new bonds found in the products are formed as the nitrogen–nitrogen bond in the hydrazoaromatic is broken, and others[4] favoring a process in which bond scission and formation occur sequentially. Even among those holding the latter view there are differences regarding the nature of the intermediate, some[4a] supporting a π complex and others[4b] arguing for a solvent-caged cation–radical pair.

Most of the product and kinetic data for the benzidine rearrangement can be equally well explained by either a concerted or a stepwise mechanism. However, *p*-semidine (*p*-aminodiphenylamine) formation is difficult to interpret in terms of the polar transition-state mechanism (the most recent proposal for the concerted process) since bond formation over a distance of about 5.3 Å would be required.[5] Indeed, *p*-semidine-type products have seldom been isolated from benzidine rearrangements[6] and in most cases in which they have been obtained the conditions were unusual. These facts have led to the suggestion[3] that *p*-semidines are not formed in the normal benzidine rearrangement. This conclusion has been used to support the polar transition state.[3] On the other hand, the formation of a *p*-semidine would be a logical outcome of the π complex or cation–radical mechanisms since the fragments resulting from nitrogen–nitrogen bond breaking would be able to assume a variety of positions with respect to each other.

A *p*-semidine-like compound has been detected among the products resulting from rearrangement of N,N′-dimethylhydrazobenzene at 25° in 25% aqueous methanol using 0.01 *M* hydrochloric acid as catalyst. Analysis was accomplished by the isotope dilution procedure. The following compounds were observed: 50.7% N,N′-dimethyl-4,4′-diaminobiphenyl (benzidine), 20.3% N,N′-dimethyl-2,4′-daminobiphenyl (diphenyline), 0.9% N,N′-dimethyl-2,2′-diaminobiphenyl (*o*-benzidine); 15.5% N,N′-dimethyl-*o*-aminodiphenylamine (*o*-semidine); 3.0% N,N′-dimethyl-*p*-aminodiphenylamine (*p*-semidine), and 11.2% N-methylaniline (disproportionation product). The benzidine and diphenyline were isolated as the N,N′-dibenzoyl derivatives, the semidines as monobenzamides, and the disproportionation product as the acetamide. These derivatives were purified by chromatography followed by several recrystallizations (often from two different solvents). From the material balance, it is obvious that essentially all of the products have been accounted for in this analysis.

The kinetics of acid-catalyzed rearrangement of N,N′-dimethylhydrazobenzene in 25% aqueous methanol at 25° were also investigated. The experimental results conform to an expression of the following type: rate = $k_2(H^+)$(substrate). The rates of isomerization of the 4,4′-dichloro and 4,4′-dimethyl derivatives of N,N′-dimethylhydrazobenzene were also determined, and the second-order rate constants for the three hydrazo compounds were correlated by σ^+ constants and a ρ value of −11.85.

The rearrangement of N,N′-dimethylhydrazobenzene is similar to the isomerization of hydrazobenzene in that the major products are the benzidine and the diphenyline.[7] The ratio of these two products is about the same in both reactions, about 2.3–2.5. However, the two rearrangements differ in that sizable amounts of both the *o*- and *p*-semidine products result from the reaction involving N,N′-dimethylhydrazobenzene. The formation of a *p*-semidine is particularly interesting since it cannot arise from con-

(1) Research supported by National Science Foundation Grant GP-1970.

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