The generality of this method for preparing other β-arabinosides for biological evaluation is currently under investigation.[12]

(12) The synthesis of 1-β-D-arabinofuranosyl-5-fluorouracil (Vc) by another route was announced by J. J. Fox, N. Yung, I. Wempen, R. Duschinsky and L. Kaplan, Abstr. Intl. Union Pure and Applied Chemistry (Symposium on Natural Products), Australia, August 1960, p. 66. Their synthesis begins with 5-fluorouridine (prepared from 5-fluorouracil) which is converted *via* a 2,2′-anhydronucleoside intermediate to Vc in 26% yield based upon 5-fluorouracil (personal communication from Fox and Yung).

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RECEIVED FEBRUARY 9, 1961

SYNTHESIS OF PHENYLCHLOROTRISPHOSPHONITRILE

Sir:

We wish to report the direct preparation and positive identification of phenylchlorotrisphosphonitrile, $[Ph(Cl)PN]_3$. Although previous workers have studied the synthesis of the $[Ph(Cl)PN]_n$ system, none has reported isolation of the trimer. Thus Bode and Bach[1] treated $PhPCl_4$ with ammonium chloride and could isolate only a partially hydrolyzed derivative for which analysis indicated the formula $N_3P_3Ph_3Cl(OH)_2$. Shaw and Stratton[2] repeated the reaction and isolated $[Ph(Cl)PN]_4$ in two isomeric forms. Herring,[3] using the novel procedure of treating NaN_3 with $PhPCl_2$, isolated a mixture of phenylchlorophosphonitriles with an average molecular weight of 5000. Recently, Tesi[4] reported synthesis of $[Me(Cl)PN]_3$ by treatment of $N_3P_3Cl_3(NMe_2)_3$ with MeMgBr to give $N_3P_3Me_3(NMe_2)_3$ which was converted to $[Me(Cl)PN]_3$ by treatment with HCl. Although this procedure gives an $[R(Cl)PN]_3$ compound, it is not a direct synthesis.

In our preparation $PhPCl_4$ was made by chlorination of $PhPCl_2$ (Victor Chemical Works) in carbon tetrachloride then recrystallization from the same solvent under dry nitrogen. A solution of 121 g. (0.484 mole) of $PhPCl_4$ in 250 ml. of dried and redistilled *s*-tetrachloroethane was added over a period of 28 hr. to a slurry of 197 g. (3.71 moles) of NH_4Cl in 50 ml. of dry xylene. Reflux was then maintained for an additional 24 hours; unreacted ammonium chloride was filtered off, washed with dry benzene, and the washes were combined with the filtrate. Concentration of the solution gave a gummy solid (I) and solution (II) which could not be separated effectively by filtration. However, addition of petroleum ether converted (I) to a solid which was filtered off and recrystallized from acetonitrile to give 8 g. of crude trimer, m.p. 135–150° (A). Solution (II) was distilled to dryness to give a hard gum which was crystallized fractionally from acetonitrile to give an additional 12 g. of crude trimer, m.p. 130–150° (B). The infrared curves of A and B were similar, showing strong absorptions in the 1200 $cm.^{-1}$ region, typical of the trimeric phosphonitrile ring. A was fractionally recrystallized three times from acetonitrile to give 3 g. of material, the analytical sample, m.p. 161–163° (Fisher-Johns block, uncorrected). *Anal.*[5] Calcd. for C_6H_5ClPN: P, 19.66; N, 8.90; C, 45.74; H, 3.20; Cl, 22.51; mol. wt. calcd. for $(C_6H_5(Cl)PN)_3$, 473. Found: P, 19.63; N, 9.01; C, 45.67; H, 3.44; Cl, 22.38; mol. wt.,[6] 445, 448. The principal P–N ring infrared absorptions are at 1180 $cm.^{-1}$ (s) and 1210 $cm.^{-1}$ (s), with no discernible absorptions at the reported values[2] for the tetramer. Infrared analysis indicated that the remainder of the reaction product contained additional trimer and also tetramer. Although recovery of trimer from this residue is difficult, procedures for its accomplishment are being investigated.

Using a different procedure, the tetramer recently has been prepared in this laboratory in better than 60% yield and this work will be reported shortly. Both trimer and tetramer now are being studied with respect to alkylation, arylation, and other substitution reactions.

We wish to thank the Armstrong Cork Company, Lancaster, Penna., for generous support of this work.

(1) H. Bode and H. Bach, *Ber.*, **75**, 215 (1942).
(2) R. A. Shaw and C. Stratton, *Chem. & Ind.*, **52** (1959).
(3) D. L. Herring, *Chem. & Ind.*, 717 (1960).
(4) G. Tesi, *Proc. Chem. Soc.*, **404** (1960).
(5) Schwartzkopf Microchemical Laboratories.
(6) Ebulliometric measurement in benzene. We are indebted to Dr. Ralph Griffith, Sinclair Research Laboratories, for this measurement.

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RECEIVED FEBRUARY 27, 1961

STEREOCHEMISTRY OF SUBSTITUTION TO ASYMMETRIC SILICON

Sir:

Since the removal of the barrier to synthesis of optically active organosilicon compounds having reactive groups bonded to asymmetric silicon, and the discovery of many stereospecific reactions at silicon,[1,2,3] one of the major remaining tasks has been stereochemical correlation of configuration for a few key compounds containing the α-naphthylphenylmethylsilyl group (α-NpPhMeSi-, designated R_3Si^*-below), in order that the stereochemistry of many reactions of these compounds might become known.

One of the most widely used methods for correlating configurations of optically active compounds having *similar* structures is the Fredga method based on *differences* in phase behavior.[4] This method as applied by K. Mislow has provided many fruitful results in recent years, and the pertinent case observed in the present work is his "case 2"[5] in which pure optical isomers of two dif-

(1) L. H. Sommer and C. L. Frye, *J. Am. Chem. Soc.*, **81**, 1013 (1959).
(2) L. H. Sommer and C. L. Frye, *ibid.*, **82**, 3796 (1960).
(3) L. H. Sommer and C. L. Frye, *ibid.*, **82**, 4118 (1960).
(4) See A. Fredga in "The Svedberg," Almqvist and Wikesells, Uppsala, 1944, p. 261, and J. Timmermans, *J. chim. phys.*, **49**, 162 (1952). Conclusions drawn on the basis of a *difference* in phase behavior without exception have proved accurate.
(5) K. Mislow and M. Heffler, *J. Am. Chem. Soc.*, **74**, 3668 (1952). For a recent application of "case 2" for determination of the configurational relationships between the pure enantiomers of 3-thioloctanedioic acid and 3-methyloctanedioic acid see K. Mislow and W. C. Meluch, *ibid.*, **78**, 5920 (1956). For other examples see J. Timmermans, ref. 4.

ferent substances that are isomorphous give solid solutions when they are of the same configuration and a eutectic when they are of opposite configuration. In the present work X-ray diffraction provided clear and consistent answers for R_3Si^*F, R_3Si^*H and R_3Si^*Cl: (1) Solid solutions are formed by $(-)R_3Si^*F$ and $(-)R_3Si^*H$; by $(-)R_3Si^*F$ and $(+)R_3Si^*Cl$; and by $(-)R_3Si^*H$ and $(+)R_3Si^*Cl$. (2) Eutectic mixtures are formed by $(+)R_3Si^*F$ and $(-)R_3Si^*H$; by $(+)R_3Si^*F$ and $(+)R_3Si^*Cl$; and by $(+)R_3Si^*H$ and $(+)R_3Si^*Cl$.

Optically active R_3Si^*H, R_3Si^*F and R_3Si^*Cl crystallize individually in the orthorhombic system with space group $P2_12_12_1$; an example of perfect isomorphism is observed. The three mixtures (1) also crystallize in the orthorhomic system and are isomorphous with the pure component compounds; no doubling of the unit cell dimensions or change in the symmetry is observed.

Extension of the above stereochemical correlations to include R_3Si^*OH and some of its derivatives was achieved through use of optical rotatory dispersion curves obtained through the kindness of Professor Stanley Kirschner, who made his apparatus available to us for use at Wayne State University.[6] Very similar curves showing negative Cotton effects[7] were obtained for $(-)R_3Si^*F$, $(-)R_3Si^*H$, $(+)R_3Si^*Cl$, $(-)R_3Si^*OCH_3$, $(-)R_3Si^*OCOCH_3$, and $(-)R_3SiOH$. Since the first three compounds have the same configuration from X-ray application of the Fredga method, and the last three are rigorously known to have the same configuration from chemical correlations of configuration,[2] it is concluded that all six compounds have the same configuration. Rotatory dispersion data for four of the compounds in cyclohexane solvent at 24° and *c.* 0.2 are given:

$(-)R_3Si^*F$; $[\alpha]_{589}-33°$, $[\alpha]_{400}-108°$, $[\alpha]_{360}-164°$, $[\alpha]_{340}-220°$, $[\alpha]_{333}-248°$, $[\alpha]_{326}-150°$, $[\alpha]_{315}-60°$

$(-)R_3Si^*H$; $[\alpha]_{589}-30°$, $[\alpha]_{400}-100°$, $[\alpha]_{360}-140°$, $[\alpha]_{340}-160°$, $[\alpha]_{333}-230°$, $[\alpha]_{315}-54°$

$(-)R_3Si^*OH$; $[\alpha]_{589}-21°$, $[\alpha]_{400}-131°$, $[\alpha]_{360}-218°$, $[\alpha]_{337}-314°$, $[\alpha]_{325}-44°$

$(-)R_3Si^*OCH_3$; $[\alpha]_{589}-15°$, $[\alpha]_{400}-60°$, $[\alpha]_{330}-102°$, $[\alpha]_{340}-133°$, $[\alpha]_{332}-157°$, $[\alpha]_{320}-63°$, $[\alpha]_{300}-40°$

All six compounds studied by rotatory dispersion have the first maximum in the ultraviolet at 317 mμ (ϵ = 310).

The stereochemical correlations of configuration resulting from the above experimental data permit the definitive formulation of the stereochemistry of the reactions of R_3Si^*X already published[1,2,3] plus some additional reactions not yet published. Reactions 1–10 proceed with *inversion*, and reactions 11–15 with *retention of configuration.*

(1) $(+)R_3Si^*Cl \xrightarrow{H_2O \text{ in } Et_2O} (+)R_3Si^*OH$

(2) $(+)R_3Si^*Cl \xrightarrow[\text{ether}]{LiAlH_4} (+)R_3Si^*H$

(3) $(+)R_3Si^*Cl \xrightarrow[\text{pentane; amine}]{MeOH} (+)R_3Si^*OCH_3$

(4) $(+)R_3Si^*F \xrightarrow[\text{ether}]{LiAlH_4} (-)R_3Si^*H$

(5) $(+)R_3Si^*Cl \xrightarrow[\text{xylene}]{KOH(s)} \xrightarrow{H_2O} (+)R_3Si^*OH$

(6) $(+)R_3Si^*Cl \xrightarrow[\text{ether}]{NaB(OCH_3)_4} (+)R_3Si^*OCH_3$

(7) $(+)R_3Si^*OH \xrightarrow[\text{xylene}]{KOH(s)} \xrightarrow[\text{xylene}]{(-)R_3Si^*Cl}$ (meso) $R_3Si^*OSi^*R_3$

(8) $(-)R_3Si^*OCH_3 \xrightarrow[NaOH]{H_2O \text{ in acetone}} (+)R_3Si^*OH$

(9) $(+)R_3Si^*—O—COC_6H_5 \xrightarrow[\text{ether}]{LiAlH_4} (-)R_3Si^*H$

(10) $(+)R_3Si^*—O—COCH_2Cl \xrightarrow[\text{pentane; amine}]{CH_3OH} (-)R_3Si^*OCH_3$

(11) $(-)R_3Si^*H \xrightarrow[CCl_4]{Cl_2} (+)R_3Si^*Cl$

(12) $(+)R_3Si^*OCH_3 \xrightarrow[\text{ether}]{LiAlH_4} (+)R_3Si^*H$

(13) $(+)R_3Si^*OSi^*R_3 \xrightarrow[\text{ether}]{LiAlH_4} (+)R_3Si^*H$

(14) $(+)R_3Si^*H \xrightarrow[\text{xylene}]{KOH(s)} \xrightarrow{H_2O} (+)R_3Si^*OH$

(15) Grignard reduction: $(+)R_3Si^*OCH_3 + t\text{-}C_4H_9MgCl \xrightarrow[24 \text{ hr.}]{95°} (+)R_3Si^*H + CH_2=C(CH_3)_2$

(16) $(-)R_3Si^*OCH_3 \xrightarrow[CH_3OH]{CH_3ONa(10^{-3}M)}$ racemization; too fast to measure

For reactions with essentially nucleophilic reagents, the above stereochemical data may be summarized in terms of leaving groups:

(1) *For good leaving groups such as -Cl or -OCOR*, whose conjugate acids have pK_a smaller than *ca.* 5, *the favored stereochemistry is inversion of configuration.*

(2) *For poor leaving groups such as -H, -OCH$_3$, or -OH*, whose conjugate acids have pK_a larger than *ca.* 10, *the predominant stereochemistry depends upon the relative importance of several factors and may be either retention or inversion of configuration in individual cases.*

The interesting complexities engendered in organosilicon stereochemistry by use of hybrid orbitals containing a 3*d* component, as revealed by

(6) S. Kirschner, A. J. Sonnessa, D. C. Bhatnagar and D. Moy, Abstracts of the 138th Meeting of the American Chemical Society, September, 1960, p. 14-N.

(7) As has been pointed out by C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., New York, N. Y., 1960, pages 102–108, correlation between rotatory dispersion curves and configuration for acyclic compounds must take into account the possibility of free-rotational "conformational" isomerization. However, this kind of uncertainty of interpretation certainly should not obtain for five of the compounds studied on the basis of examination of accurately scaled molecular models and, in fact, does not obtain even in the case of R_3Si^*Cl.

the present work and previous studies of bridgehead silicon, will be dealt with at length in a later full article.

We thank Dow Corning Corporation for continued generous support.

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RECEIVED MARCH 30, 1961

STEREOSPECIFICITY IN A NEW TYPE OF SYNTHETIC ANTITUBERCULOUS AGENT[1,2]

Sir:

We wish to report the synthesis of a new highly-active antituberculous compound, the dextrorotatory form of 2,2′-(ethylenediimino)-di-1-butanol (ethambutol),[3] which is four times as active as streptomycin against an established infection with the human strain of *Mycobacterium tuberculosis* in mice. It is also fully active against isoniazid-resistant infections as well as against streptomycin-resistant infections in mice. The sharp stereospecificity of the activity of this synthetic chemotherapeutic agent (*dextro* = 12 × *meso* = >200 × *levo*) contrasts with the equality in acute toxicity of the stereoisomers in mice. The high efficacy index (ratio of tolerance to potency) of this compound has warranted its clinical trial, the results of which will be reported elsewhere.

The experimental chemotherapeutic study of the stereoisomers of 2,2′-(ethylenediimino)-di-1-butanol in comparison with streptomycin and isoniazid is summarized in the table. The antituberculous activity of these isomers varied considerably with the configuration at the asymmetric carbons, the *levo* isomer being inactive at the maximum tolerated dose (at least a 200-fold difference in activity). The one center with the dextrorotatory configuration in the *meso* isomer appears to be the source of its activity even though it is considerably less than half as active as the *dextro* form, both *in vivo* and *in vitro*. In contrast, the acute lethal toxicity in mice of the three isomers and the racemate is the same within experimental error. The reason for the remarkable stereospecificity in this synthetic antibacterial agent is under study. (+)-2,2′-(Ethylenediimino)-di-1-butanol showed no activity against lethal infections with Gram-negative and Gram-positive organisms in mice. The high antibacterial specificity also was confirmed by the lack of activity *in vitro* against these organisms or against various fungi.

(+)-2,2′-(Ethylenediimino)-di-1-butanol also was highly effective using delayed treatment of an established mycobacterial infection of mice. In addition, the activity against infections with mycobacteria resistant to current drugs has been demonstrated clearly. Against a lethal infection in mice with a human strain resistant to the maximum tolerated dose of streptomycin, this new agent was fully as active parenterally as against the strains sensitive to this drug. The same was true of oral treatment in a lethal infection with a bovine strain resistant to the maximum tolerated dose of isoniazid. Equally important is the fact that repeated growth *in vitro* in its presence has failed so far to show the development of resistance to this substance by the human strain of *Mycobacterium tuberculosis*, $H37R_v$.

CHEMOTHERAPEUTIC EVALUATION OF STEREOISOMERS OF 2,2′-(ETHYLENEDIIMINO)-DI-1-BUTANOL·2HCl

	Oral treatment[a]			Subcutaneous treatment[a]		
	ED_{50}[b]	Max. tol. dose[c]	Efficacy index[d]	ED_{50}[b]	Max. tol. dose[c]	Efficacy index[d]
(−)-Isomer	Inactive[e]	6400		Inactive[e]	800	
meso Form	500	6400		500	800	
(±)-Form	90	6400		90	800	
(+)-Isomer	45	6400	120	45	800	18
Streptomycin				80	400	5
Isoniazid	1.2	100	80			

[a] Administration by daily single dosage. [b] Estimated median effective dose (in mg./kg./day administered for 14 days from day of infection) required for 60 day survival where all infected untreated control mice died in an average time of 17 days. The infecting organism was the human strain of *Mycobacterium tuberculosis*, $H37R_v$. [c] The maximum tolerated dose is the amount in mg./kg./day administered for 14 days which gave about 10% weight loss after one week. [d] Ratio of maximum tolerated dose to median effective dose. [e] Inactive at the maximum tolerated dose.

The highly active (+)-isomer was prepared by brief heating of ethylene dichloride with excess (+)-2-amino-1-butanol.[4] A 42% yield of purified (+)-2,2′-(ethylenediimino)-di-1-butanol (m.p. base[5] 87.5–88.8°, m.p. dihydrochloride[6] 198.5–200.3°) was obtained after removal of the less soluble *meso* isomer (m.p. base 135.8–136.5°; m.p. dihydrochloride 203.5–204.6°) corresponding to approximately the amount of *levo* impurity in the (+)-2-amino-1-butanol. The *levo* diamine (m.p. base[7] 89–90°; m.p. dihydrochloride[8] 200.5–201.5°) was prepared in the same way from (−)-2-amino-1-butanol[4] in 52% yield. When (±)-2-aminobutanol reacted with either ethylene chloride, ethylene bromide or ditosyl glycol, the condensation occurred most rapidly at the temperature obtained without solvent, although a longer time at lower temperature (alcohol) has given comparable results. The main products, each isolated in about 40% yield, are the racemic base (m.p. 75–76°; b.p. 160–170° (0.3 mm.); dihydrochloride m.p. 179–180°) and the *meso* diamine. These were separated readily as a result of the low solubility of the latter in a number of solvents. The racemic and *meso* isomers of β,β′-diethyl-1,4-piperazine-

(1) Additional data will be published by Thomas, Baughn, Wilkinson and Shepherd, *Am. Rev. Resp. Dis.*, 1961.

(2) We wish to acknowledge the valuable assistance of Drs. S. Kushner and H. J. White of these Laboratories.

(3) Ethambutol is the generic name reserved for this isomer by the Lederle Laboratories Division of the American Cyanamid Company.

(4) From commercial (±)-2-aminobutanol by the tartrate resolution procedure of F. H. Radke, R. B. Fearing and S. W. Fox, *J. Am. Chem. Soc.*, **76**, 2801 (1954).

(5) *Anal.* Calcd.: 58.8% C, 11.8% H, 13.7% N. Found: 58.8% C, 12.1% H, 13.7% N.

(6) α_D^{25} +5.5° ± 0.4 (H_2O). *Anal.* Calcd.: 43.3% C, 9.5% H, 10.1% N, 25.6% Cl. Found: 43.5% C, 9.7% H, 10.4% N, 25.6% Cl.

(7) *Anal.* Found: 58.5% C, 12.0% H, 13.8% N.

(8) α_D^{25} −4.7 ± 0.4° (H_2O). *Anal.* Found: C, 43.5; H, 9.5; N, 10.2%; Cl, 25.4%.