ium compounds react with the silicon–hydrogen group in diethyl ether to give tetrasubstituted products. Triethylsilane[1a,b] has been found to react with methyl-, *n*-propyl-, *n*-butyl- and phenyllithium to give the respective tetrasubstituted organosilicon compounds. Triphenylsilane[2] also has been found to react similarly.

Nebergall[3] has shown that phenylsilane reacts with an excess of phenyllithium and ethyllithium in diethyl ether to give tetraphenylsilane and triethylphenylsilane, respectively. That the solvent plays an important role in the reaction was demonstrated when excess ethyllithium was treated with phenylsilane in petroleum ether. The product from this reaction was diethylphenylsilane. Nebergall reported that no reaction occurred between phenylsilane and a large excess of phenylmagnesium bromide in diethyl ether.

Triphenylsilane[2] has been found to be unreactive toward phenylmagnesium bromide in ether, refluxing xylene, and a mixture of ether and dioxane. West and Rochow[4] have reported that di-*n*-butylsilane does not react with ethylmagnesium bromide in a mixture of ether and toluene at 100°.

One of the steps in the cleavage[5] of symmetrical diphenyldisiloxane with Grignard reagents in diethyl ether has been shown to lead to alkylation of the silicon–hydrogen group.

We have found that triphenylsilane, diphenylsilane, and phenylsilane will react with Grignard reagents in tetrahydrofuran (THF). Triphenylsilane reacted with phenylmagnesium bromide, after 24 hours of refluxing in THF, to give a 14% yield of tetraphenylsilane which was identified by infrared spectrum and by mixed melting point with an authentic sample. Triphenylsilane also gave allyltriphenylsilane in a 53% yield when treated for 24 hours with allylmagnesium chloride[6] in refluxing THF.

Diphenylsilane when allowed to react with excess phenylmagnesium bromide for a period of two days in refluxing THF gave a 79% yield of triphenylsilane. Diphenylsilane also reacted with excess *n*-butylmagnesium bromide under similar conditions to give a 72% yield of *n*-butyldiphenylsilane, b.p. 110–112° (1 mm.), $n^{20}D$ 1.5541, d^{20}_4 0.9604. *Anal.* Calcd. for $C_{16}H_{21}Si$: Si, 11.68; MR, 80.17. Found: Si, 11.53, 11.52; MR, 80.24. Refluxing a solution of diphenylsilane with an excess of phenylmagnesium bromide in diethyl ether gave a 31% yield of triphenylsilane.

Phenylsilane after reaction with one equivalent of phenylmagnesium bromide in THF at room temperature for 6.5 hours gave a 66% yield of diphenylsilane; while the same reaction, when carried out in diethyl ether at room temperature for 24 hours, gave a 52% yield of diphenylsilane. Likewise, phenylsilane reacted with one equivalent of *n*-dodecylmagnesium bromide in THF to give a 78% yield of *n*-dodecylphenylsilane, b.p. 130–131° (0.6 mm.), $n^{20}D$ 1.4480, d^{20}_4 0.8629. *Anal.* Calcd. for $C_{18}H_{32}Si$: Si, 10.16; *MR*, 92.29. Found: Si, 10.13, 9.99; *MR*, 92.41.

n-Dodecylphenylsilane, prepared as previously stated, reacted with one equivalent of benzylmagnesium chloride, after refluxing for 18 hours in THF, to give a 63% yield of benzyl-*n*-dodecylphenylsilane, b.p. 180–183° (0.12 mm.), $n^{20}D$ 1.5233, d^{20}_4 0.9209. *Anal.* Calcd. for $C_{25}H_{38}Si$: Si, 7.66; MR, 121.05. Found: Si, 7.59, 7.62; MR, 121.68.

Related reactions, with a variety of RM compounds, are in progress with other combinations having one or more hydrogens attached to various metals and metalloids. Some dialkylsilanes appear to behave differently than the diarylsilanes.

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DEPARTMENT OF CHEMISTRY
IOWA STATE COLLEGE HENRY GILMAN
AMES, IOWA ERNEST A. ZUECH

RECEIVED JULY 1, 1957

(1) (a) H. Gilman and S. P. Massie, Jr., THIS JOURNAL, **68**, 1128 (1946); (b) R. N. Meals, *ibid.*, **68**, 1880 (1946).

(2) H. Gilman and H. W. Melvin, Jr., *ibid.*, **71**, 4050 (1949).

(3) W. H. Nebergall, *ibid.*, **72**, 4702 (1950).

(4) R. West and E. G. Rochow, *J. Org. Chem.*, **18**, 302 (1953).

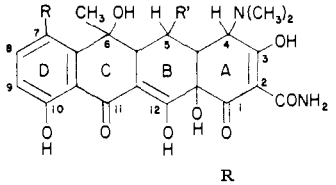
(5) M. C. Harvey, W. H. Nebergall and J. S. Peake, THIS JOURNAL, **79**, 1437 (1957).

(6) Unpublished studies of Theodore Soddy in this Laboratory have indicated that triphenylsilane will not react with allylmagnesium chloride in diethyl ether.

A NEW FAMILY OF ANTIBIOTICS: THE DEMETHYLTETRACYCLINES

Sir:

Among the most useful of the broad-spectrum antibiotics is a small group of substances derived from perhydronaphthacene and called the tetracyclines. Tetracycline, 7-chlorotetracycline, and 5-hydroxytetracycline[1] are used in therapy.



	R	R'
Tetracycline	H	H
7-Chlorotetracycline	Cl	H
5-Hydroxytetracycline	H	OH

We now wish to describe four members of a new family of compounds closely related to the previously known tetracyclines. On the basis of physical and chemical properties presented here and on the basis of degradation studies presented in the accompanying papers, it has been established that these four new compounds are 6-demethyltetracycline (I), 7-chloro-6-demethyltetracycline (II), 6-demethyl-4-*epi*-tetracycline (III), and 7-chloro-6-demethyl-4-*epi*-tetracycline (IV). 6-Demethyltetracycline hydrochloride hemihydrate: $[\alpha]^{25}D$ −259° (0.5% in 0.1 *N* H_2SO_4); m.p., dec. 203–209°; *Anal.* Calcd. for $C_{21}H_{24}N_2ClO_{8.5}$: C, 53.00; H, 5.08; N, 5.89; Cl, 7.45; O, 28.58; H_2O, 1.89. Found: C, 52.52; H, 5.34; N, 6.05;

(1) The trademarks of the American Cyanamid Company for tetracycline and 7-chlorotetracycline are Achromycin and Aureomycin, respectively. The trademarks of Chas. Pfizer and Co., Inc., for tetracycline and 5-hydroxytetracycline are Tetracyn and Terramycin, respectively.

Cl, 7.51; O, 28.58 (diff.); H_2O, 1.96. 7-Chloro-6-demethyltetracycline sesquihydrate: $[\alpha]^{25}D$ −258° (0.5% in 0.1 *N* H_2SO_4); m.p., dec. 174–178°; *Anal.* Calcd. for $C_{21}H_{24}N_2ClO_{9.5}$: C, 51.27; H, 4.92; N, 5.70; Cl, 7.21; O, 30.90; H_2O, 5.49. Found: C, 51.13; H, 4.93; N, 6.00; Cl, 7.39; O, 30.55 (diff.); H_2O, 4.45. 6-Demethyl-4-*epi*-tetracycline hydrochloride: $[\alpha]^{25}D$ −335° (0.5% in 0.1 *N* H_2SO_4); m.p., dec. 225–230°; *Anal.* Calcd. for $C_{21}H_{23}N_2ClO_8$: C, 54.02; H, 4.97; N, 6.00; Cl, 7.61; O, 27.42. Found: C, 54.56; H, 5.19; N, 6.07; Cl, 7.67; O, 26.51 (diff.). 7-Chloro-6-demethyl-4-*epi*-tetracycline hydrochloride: $[\alpha]^{25}D$ −323° (0.5% in 0.1 *N* H_2SO_4); m.p., dec. 214–216°; *Anal.* Calcd. for $C_{21}H_{22}N_2Cl_2O_8$: C, 50.31; H, 4.42; N, 5.59; Cl, 14.15; O, 25.53. Found: C, 50.38; H, 4.81; N, 5.28; Cl, 14.21; O, 25.32 (diff.).

TABLE I

R_f VALUES IN PAPER CHROMATOGRAPHIC SYSTEMS[a]

	0.3*M* sodium phosphate/ *n*-butanol (*p*H 3.0)	Mac-Ilvaine's buffer/ ethyl acetate (*p*H 4.7)	0.3*N* H_3PO_4/ 0.1% CCl_3COOH 9:1 $CHCl_3$ —*n*-BuOH (*p*H 1.9)
7-Chlorotetracycline	0.59	0.78	0.61
7-Chloro-4-*epi*-tetracycline	.59	.28	.33
7-Bromotetracycline	.59	.78	.61
7-Bromo-4-*epi*-tetracycline	.59	.28	.33
7-Chloro-6-demethyltetracycline (II)	.47	.70	.39
7-Chloro-6-demethyl-4-*epi*-tetracycline (IV)	.47	.26	.20
5-Hydroxytetracycline	.37	.60	.23
5-Hydroxy-4-*epi*-tetracycline	.37	.03	.11
Tetracycline	.37	.46	.20
4-*epi*-Tetracycline	.37	.15	.12
6-Demethyltetracycline (I)	.30	.27	.22
6-Demethyl-4-*epi*-tetracycline (III)	.30	.09	.10

[a] These values were determined using pure components. The components may migrate differently when present in crude fermentation mixtures, the migration rates being influenced by salts, natural carriers, etc.

TABLE II

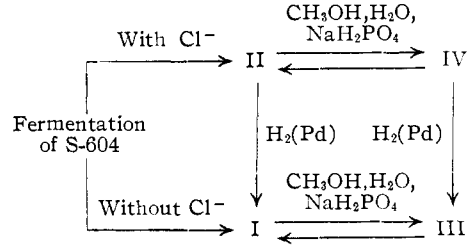
COMPARISONS OF STABILITIES TOWARD ACID AND BASE AND OF *in Vitro* ANTIBACTERIAL ACTIVITIES

	Half destruction time (min.) in: 1.0 *N* H_2SO_4 at 100°	0.1 *N* NaOH at 100°	% of *in vitro* antibact-activ. of 7-chlorotetracycline against *S. aureus* (turbidimetric meas.)
7-Chloro-6-demethyltetracycline (II)	445	40	75
7-Chlorotetracycline	2.1	<0.3	100
7-Chloro-6-demethyl-4-*epi*-tetracycline (IV)	322	35.6	7
7-Chloro-4-*epi*-tetracycline	5.8	<0.6	4.2
6-Demethyltetracycline (I)	24.8	31.5	24
Tetracycline	1.0	6.8	25
6-Demethyl-4-*epi*-tetracycline (III)	25.8	46	3
4-*epi*-Tetracycline	0.9	7.2	1.6
5-Hydroxytetracycline	4.5	2.2	24
5-Hydroxy-4-*epi*-tetracycline	2.6	3.3	1.1

Additional constants obtained on II hydrochloride were: Calcd.: N-methyl, for one dimethylamino group, 6.0; O-methyl, 0; O, 25.54. Found: N-methyl, 7.4; O-methyl, 0; O, 26.2 (Unterzaucher).

Compounds I and II are produced by a mutant of *Streptomyces aureofaciens* Duggar, coded as Mutant S-604 and derived ultimately from the original 7-chlorotetracycline-producing *S. aureofaciens* A-377 soil isolate of Duggar. Compounds III and IV are derived from I and II, respectively, by a process analogous to that used in the conversion of the previously known tetracyclines to their epimers.[2] Differentiation of these new compounds from each other and from the previously known tetracyclines can be accomplished by paper chromatography (Table I). The ultraviolet absorption spectra of these new compounds are essentially unchanged from those of their previously known 6-methyl analogs. A striking feature of all four new compounds is their great resistance to degradation by acid or by alkali. Comparisons are given in Table II. Relative *in vitro* antibacterial activities against *Staphylococcus aureus* are presented in Table II.[3]

The inter-relationships of these 6-demethyltetracyclines are established by the following observations. Catalytic hydrogenation (palladium on charcoal, 1.1 atm. of hydrogen) of II yields I and of IV yields III. Chloride-containing fermentations produce predominantly II; chloride-free fermentations produce I.[4] I and III are reversibly interconvertible under epimerizing conditions and II and IV behave analogously. Assignment of configuration at C.4, relative to the tetracyclines, was made on the basis of ultraviolet and infrared



spectra, antibacterial activity, and paper chromatographic behavior.

The great resistance of these new compounds to degradation by acid or by alkali was interpreted as meaning that the common difference between the new compounds and the previously known tetracyclines lay in Ring C, since degradation by acid and degradation by alkali both involve initially Ring C.[5,6,7,8] The ultraviolet absorption spectra,

(2) A. P. Doerschuk, B. A. Bitler and J. R. D. McCormick, THIS JOURNAL, **77**, 4687 (1955).

(3) This brings to three the number of positions in the tetracycline molecule at which a simple change of substituents has been possible without an appreciable reduction of the *in vitro* antibacterial activity against *S. aureus* from that of tetracycline: C.5, H to OH; C 6, CH_3 to H; C.7, H to Cl or Br. Other simple changes, such as 2-carboxamido to 2-cyano or inversion of C.4 configuration, diminish this activity by twenty-fold or greater.

(4) A. P. Doerschuk, J. R. D. McCormick, J. J. Goodman, S. A. Szumski, J. A. Growich, P. A. Miller, B. A. Bitler, E. R. Jensen, M. A. Petty and A. S. Phelps, THIS JOURNAL, **78**, 1508 (1956).

(5) C. W. Waller, B. L. Hutchings, R. W. Broschard, A. A. Goldman, W. J. Stein, C. F. Wolf and J. H. Williams, *ibid.*, **74**, 4981 (1952).

(6) C. W. Waller, B. L. Hutchings, C. F. Wolf, A. A. Goldman, R. W. Broschard and J. H. Williams, *ibid.*, **74**, 4981 (1952).

(7) F. A. Hochstein, C. R. Stephens, L. H. Conover, P. P. Regna,

which are essentially superimposable on those of the corresponding 6-methylated tetracyclines, showed that the Rings B–C–D chromophore was not changed,[7,8] leaving carbons 5a and 6 as possible points of difference.

R. Pasternack, P. N. Gordon, F. J. Pilgrim, K. J. Brunings and R. B. Woodward, THIS JOURNAL, **75**, 5455 (1953).

(8) C. R. Stephens, L. H. Conover, R. Pasternack, F. A. Hochstein, W. T. Moreland, P. P. Regna, F. J. Pilgrim, K. J. Brunings and R. B. Woodward, *ibid.*, **76**, 3568 (1954).

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ELMER R. JENSEN
ALBERT P. DOERSCHUK

RECEIVED AUGUST 1, 1957

DEMETHYLTETRACYCLINES. STRUCTURE STUDIES

Sir:

The isolation and characterization of a new series of highly active tetracycline antibiotics has been reported recently.[1] In this communication degradation studies are presented showing that the parent compound of this series is 6-demethyltetracycline.[2]

In a preliminary experiment 7-chloro-6-demethyltetracycline (I) was distilled with a highly active zinc dust[3] giving naphthacene ($\lambda_{max.}^{CHCl_3}$, 420 mμ, 446 mμ, 477 mμ). Under the same conditions chlorotetracycline gave a distillate whose ultraviolet spectrum [$\lambda_{max.}^{CHCl_3}$, 425 mμ (broad), 452 mμ (broad), 476 mμ, 485 mμ] was indicative of a mixture of naphthacene and 5-methylnaphthacene. These data coupled with the analytical results[1] indicating that these new antibiotics had one less carbon atom than the known tetracyclines[4] suggested that the C.6 methyl group of the tetracycline nucleus was missing in the new series. This was confirmed immediately by numerous Kuhn–Roth determinations on I and related compounds, all of which gave zero values. In this determination the familar tetracyclines all gave appreciable C-methyl values.[4b,5]

That the structure of I was the same as chlorotetracycline in all other respects[6] was shown by several reactions. Heating in concentrated hydrochloric acid aromatized the C ring of I giving an anhydro compound (II) in good yield, $[\alpha]^{25}D$ +105° (0.467% in methyl cellosolve); m.p. 205–210° (dec.), (*Anal.* Calcd. for $C_{21}H_{19}N_2O_7Cl$: C, 56.44; H, 4.29; N, 6.27; Cl, 7.94. Found: C, 56.39; H, 4.60; N, 5.83; Cl, 7.81; *C-methyl, 0.0*). This was considered to be good evidence for an hydroxyl group on C.6 and a hydrogen atom on C.5a. The ultraviolet absorption spectrum of II [$\lambda_{max.}^{0.1\,N\,HCl}$, 223 mμ (ε 30,200), 272 mμ (ε 52,500), 430 mμ (ε 8,050)] was quite similar to the known anhydrotetracyclines[7] but exhibited a hypsochromic shift characteristic of an aromatic compound having one less alkyl substituent.[8] The acid stability of II eliminated the possibility of C.5 bearing an hydroxyl group.[4b]

That I and the known tetracyclines have the same A ring, was shown by oxidation of I in *N* NaOH with oxygen to give dimethylamine and 3,4 - dihydroxy - 2,5 - dioxocyclopentane - 1 - carboxamide[9a] (III) identical with the compound obtained similarly from tetracycline and chlorotetracycline.[7b] From the same reaction was obtained a new compound (IV), $[\alpha]^{25}D$ +2.5° (2.00%, methanol), m.p. 194–195° (*Anal.* Calcd. for $C_{13}H_{11}O_7Cl$: C, 49.62; H, 3.52; Cl, 11.27. Found: C, 49.88; H, 3.80; Cl, 11.26; *C-methyl, 0.0*). On treatment of IV with diazomethane, a methoxydimethyl ester (V) was formed, m.p. 119.5–120.5° (*Anal.* Calcd. for $C_{16}H_{17}O_7Cl$: C, 53.86; H, 4.80; Cl, 9.94; CH_3O, 26.10. Found: C, 53.59; H, 5.08; Cl, 10.12; CH_3O, 26.66). Compound V was hydrolyzed to a methoxydiacid (VI), m.p. 210–217° (*Anal.* Calcd. for $C_{14}H_{13}O_7Cl$: C, 51.15; H, 3.98; Cl, 10.79. Found: C, 50.82; H, 4.09; Cl, 10.9) which was converted to a methoxy anhydride (VII), m.p. 242.5–243° (*Anal.* Calcd. for $C_{14}H_{11}O_6Cl$: C, 54.12; H, 3.57; Cl, 11.41. Found: C, 54.16; H, 3.82; Cl, 11.56). The infrared absorption spectrum of this latter compound had bands typical of a glutaric anhydride. Compounds IV–VII had ultraviolet and infrared absorption spectra characteristic of phthalides. Since acid permanganate oxidation of IV gave tricarballylic acid[9b] in good yield, it was postulated that IV is β-(4-chloro-7-hydroxyphthalide-3)-glutaric acid, corresponding to the 3-methyl compound[9] obtained in similar fashion from chlorotetracycline[7b] thus indicating that the B rings of both compounds must be the same. With the isolation of dimethylamine, III and IV the 21 carbons and 2 nitrogens in I were accounted for.

Proof that the D rings of I and of chlorotetracycline were the same and also confirmation of the tertiary nature of C.6 in I was obtained by a series of reactions used in a degradation of chlorotetracycline.[4a] Reduction of I with zinc dust and acetic acid yielded a dedimethylaminodeoxy compound (VIII), m.p. 212–217° (dec.) (*Anal.* Calcd. for $C_{19}H_{16}O_7NCl$: C, 56.23; H, 3.97; N, 3.45; Cl, 8.74. Found: C, 56.20; H, 3.66; N, 3.80; Cl,

(1) J. R. D. McCormick, N. O. Sjolander, U. Hirsch, E. R. Jensen and A. P. Doerschuk, THIS JOURNAL, **79**, 4561 (1957).

(2) The experiments reported herein were carried out on 7-chloro-6-demethyltetracycline. Its relationship to the parent compound and also to the 4-*epi*-isomers has been established in reference 1.

(3) (a) F. Kögl and W. B. Deijs, *Ann.*, **515**, 19 (1935). (b) We are indebted to Dr. J. B. Patrick for recommending this preparation.

(4) (a) C. R. Stephens, L. H. Conover, R. Pasternack, F. A. Hochstein, W. T. Moreland, P. P. Regna, F. J. Pilgrim, K. J. Brunings and R. B. Woodward, THIS JOURNAL, **76**, 3568 (1954); (b) F. A. Hochstein, C. R. Stephens, L. H. Conover, P. P. Regna, R. Pasternack, P. N. Gordon, F. J. Pilgrim, K. J. Brunings and R. B. Woodward, *ibid.*, **75**, 5455 (1953); (c) J. H. Boothe, J. Morton, II, J. P. Petisi, R. G. Wilkinson and J. H. Williams, *ibid.*, **75**, 4621 (1953).

(5) Unreported analyses from These Laboratories; for example, chlorotetracycline hydrochloride ($C_{22}H_{24}N_2O_8Cl_2$): Calcd. for 1 C-methyl, 2.92; Found: 1.93, 1.81, 1.91.

(6) The configurations about the five asymmetric centers in I and chlorotetracycline have not been related. However, it seems probable that they are the same in view of the high antibiotic activity of I and the strict configurational requirements for activity already demonstrated. *Cf.* A. P. Doerschuk, B. A. Bitler and J. R. D. McCormick, THIS JOURNAL, **77**, 4687 (1955), and footnote 3 of reference 1.

(7) (a) C. W. Waller, B. L. Hutchings, R. W. Broschard, A. A. Goldman, W. J. Stein, C. F. Wolf and J. H. Williams, *ibid.*, **74**, 4981 (1952). (b) J. H. Boothe, J. Morton, II, J. P. Petisi, R. G. Wilkinson, and J. H. Williams, "Antibiotics Annual 1953–1954," Welch and Martí-Ibañez, Medical Encyclopedia, Inc., New York, N. Y., p. 46.

(8) F. Korte, *Angew. Chem.*, **63**, 375 (1951).

(9) (a) C. W. Waller, B. L. Hutchings, C. F. Wolf, R. W. Broschard A. A. Goldman and J. H. Williams, THIS JOURNAL, **74**, 4978 (1952); (b) B. L. Hutchings, C. W. Waller, S. Gordon, R. W. Broschard, C. F. Wolf, A. A. Goldman and J. H. Williams, *ibid.*, **74**, 3710 (1952).