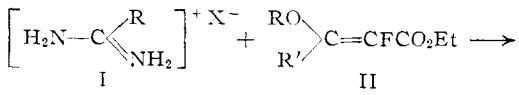
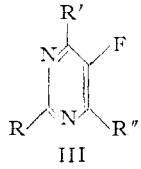


I II



III

I	a	b	c	II	a	b	c	d
R =	SEt	OMe	SMe	R =	K	Na	K	H
X =	Br	Cl	$^1/_2SO_4$	R′ =	H	H	CO_2Et	CH_2F

III	a	b	c	d	e	f	g	h	i	j	k	l
R =	SEt	OH	OMe	SMe	SH	SEt	SEt	OH	SEt	OH	SMe	OH
R′ =	OH	OH	OH	OH	OH	Cl	NH_2	NH_2	OH	OH	OH	OH
R″ =	H	H	H	H	H	H	H	H	CO_2Et	CO_2H	CH_2F	CH_2Cl

ture stand at 25° for 16 hours.[2] After IIa was refluxed for 2 hours with 0.6 moles of Ia and 0.6 moles of sodium methoxide in 1440 ml. of ethanol, evaporation, extraction with water and acidification gave IIIa (24% yield from IV), m.p. 192–193° dec. (recrystallized from ethyl acetate) (Calcd. for $C_6H_7FN_2OS$: C, 41.38; H, 4.05; F, 10.91. Found: C, 41.45; H, 4.25; F, 11.48.) Hydrochloric acid hydrolysis[1] of IIIa afforded 72% of 5-fluorouracil (IIIb), m.p. 282–283° dec., $\lambda_{max}^{0.1N\ HCl}$ 265–266 mμ (ε 7070)[3] (Calcd. for $C_4H_3FN_2O_2$: C, 36.93; H, 2.32; F, 14.61. Found: C, 37.07; H, 2.30; F, 14.69). Similarly Ib and IIa gave IIIc, m.p. 206–207° dec. (Calcd. for $C_5H_5FN_2O_2$: C, 41.67; H, 3.50; OCH_3, 21.63; F, 13.18. Found: C, 42.01; H, 3.87; OCH_3, 21.70; F, 13.51). This was hydrolyzed to yield IIIb. Hydrogenation of IIIb (1 mole hydrogen) with palladium charcoal in 2 moles of sodium hydroxide yielded 80% of uracil, whereas rhodium catalyst[4] in acetic acid produced a mixture from which 6.5% of 5-fluorodihydrouracil, m.p. 237–238° dec. (Calcd. for $C_4H_5FN_2O_2$: C, 36.37; H, 3.82; F, 14.38. Found: C, 36.32; H, 3.43; F, 14.59) was isolated by cellulose powder chromatography.[5] Condensation of Ic and IIa gave IIId, m.p. 241–243° dec. (Calcd. for $C_5H_5FN_2OS$: C, 37.49; H, 3.15; N, 17.49. Found: C, 37.98; H, 3.44; N, 17.52) which on demethylation[6] afforded 49% of IIIe, m.p. 227–229° dec. (Calcd. for $C_4H_3FN_2OS$: C, 32.87; H, 2.07; F, 13.00; Found: C, 33.45; H, 2.36; F, 12.78). Chlorination[7] of IIIa produced oily IIIf, which by autoclaving (12 hours, 100°) with liquid ammonia gave IIIg, m.p. 94°, in 88% over-all yield (Calcd. for $C_6H_8FSN_3$: C, 41.60; H, 4.66; N, 24.26. Found: C, 41.43; H, 4.73; N, 23.96). Hydrobromic acid hydrolysis of IIIg afforded 52% of 5-fluorocytosine (IIIh), m.p. 295–297° dec., $\lambda_{max}^{0.1N\ HCl}$ 285 mμ (ε 8900) (Calcd. for $C_4H_4FN_3O$: C, 37.21; H, 3.12; F, 14.72. Found: C, 36.92; H, 3.07; F, 14.47).

Diethyl oxalate (2 moles), potassium ethoxide and IV gave IIc[8] (Calcd. for $C_8H_{10}FKO_5$: C, 39.34; H, 4.12; K, 16.01; F, 7.78. Found: C, 39.03; H, 4.34; K, 16.48; F, 7.59). Condensation (as described for IIa) of Ia and IIc yielded, after processing IIIi (23% from IV), m.p. 168–169° dec. (Calcd. for $C_9H_{11}FN_2O_3S$: C, 43.89; H, 4.50. Found: C, 43.96; H, 4.61). Hydrochloric acid hydrolysis of IIIi yielded 88% of 5-fluoroörotic acid monohydrate (IIIj) m.p. 255° dec., $\lambda_{max}^{0.1N\ HCl}$ 284–285 mμ (ε 7100)[3] (Calcd. for $C_5H_3FN_2O_4,H_2O$: C, 31.26; H, 3.13; F, 9.89. Found: C, 31.36; H, 2.95; F, 10.11), which on refluxing in Dowtherm yielded 86% of IIIb.[9] Condensation of Ic and IId[10] (2 moles sodium methoxide) gave IIIk m.p. 221–222° dec. which was impure, due to partial loss of side chain fluorine (Calcd. for $C_6H_6F_2N_2OS$: C, 37.49; H, 3.15; F, 19.77. Found C, 37.68; H, 2.79; F, 13.01). This upon refluxing with hydrochloric acid yielded III (40% over-all yield from IId) m.p. 240–241° dec. (Calcd. for $C_5H_4ClFN_2O_2$: C, 33.63; H, 2.26; Cl, 19.86; F, 10.64. Found: 34.03; H, 2.11; Cl, 19.47; F, 10.64).

5-Fluorouracil and 5-fluoroörotic acid have profound activity[11] against bacteria *in vitro* and against several transplanted tumors in animals. The former is under clinical investigation in neoplastic diseases.

We are indebted to Mrs. Ellen Chiamulera for technical assistance and to Dr. Al Steyermark for the microanalyses.

(2) The compound is impure and unstable; it should be used without undue delay in the next step. In a similar run with sodium ethoxide the obtained IIb was converted by treatment with ethanolic hydrochloric acid at 25° into ethyl fluoromalonaldehydate diethyl acetal (9.3% from IV), b.p. 115–118° (24 mm.), $n^{25}D$ 1.4041. (Calcd. for $C_9H_{17}FO_4$: C, 51.91; H, 8.23; F, 9.12; OC_2H_5, 64.92. Found: C, 52.19; H, 8.38; F, 9.02; OC_2H_5, 64.55.)

(3) Data supplied by Dr. A. Motchane.

(4) W. E. Cohn and D. G. Doherty, THIS JOURNAL, **78**, 2863 (1956).

(5) The upper phase of a mixture of ethyl acetate, water, formic acid (60:35:5) was used as eluant. *Cf.* K. Fink, R. E. Cline, R. B. Henderson and R. M. Fink, *J. Biol. Chem.*, **221**, 430 (1956). The collaboration of Mr. W. E. Oberhansli in the chromatographic work is gratefully acknowledged.

(6) H. W. Barrett, I. Goodman and K. Dittmer, THIS JOURNAL, **70**, 1755 (1948).

(7) H. L. Wheeler and T. B. Johnson, *Am. Chem. J.*, **29**, 496 (1903).

(8) *Cf.* I. Blank, J. Mager and E. D. Bergmann, *J. Chem. Soc.*, 2192 (1955).

(9) This method produced 2-C^{14} labeled IIIb from Ia via IIIj.

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(11) C. Heidelberger, N. K. Chaudhuri, P. Danneberg, D. Mooren, L. Griesbach, R. Duschinsky, R. J. Schnitzer, E. Pleven and J. Scheiner, *Nature*, **179**, 663 (1957).

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RECEIVED JULY 1, 1957

SOME SELECTIVE REACTIONS OF THE SILICON-HYDROGEN GROUP WITH ORGANOMETALLIC COMPOUNDS

Sir:

We are reporting a series of reactions which readily make available the synthesis of a wide variety of organosilicon compounds, particularly those of an unsymmetrical nature. The introduction of the various R groups can be effected stepwise by the proper choice of solvent and organometallic compound. The synthesis is particularly appropriate for the preparation of low-melting organosilicon compounds of the type R_4Si where all of the R groups can be different.

Previous reports have shown that organolith-

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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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).

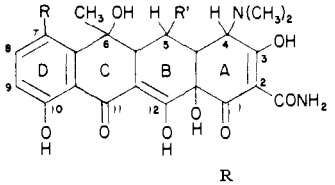
(5) M. C. Harvey, W. H. Nebergall and J. S. Peake, THIS JOURNAL, **79**, 1437 (1957).

(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.