[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY, SCHOOL OF MEDICINE, YALE UNIVERSITY]

A Comparison of the Effect of Certain Sulfur Substituents upon Acidity in the Benzene and 6-Uracil Series[1]

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The acid dissociation constants of the uracil residues in 6-uracilsulfonic acid, 6-uracil methyl sulfone and 6-uracilsulfonamide were determined at 25°. These sulfur-containing substituents were found to exert a profound influence on the uracil dissociation. A simple plot involving log K/K° for the sulfonate and sulfone derivatives of benzoic acid, phenol and uracil demonstrated the presence of a straight-line relationship between the relative acidifying effect of these substituents in either the *para* position of the benzene derivatives or the 6-position of uracil. The relationship also indicated the presence of an orderly deviation from the ideal Hammett equation. From an approximation of the dependence of σ on ρ, an apparent ρ value of 4.10 for uracil with respect to these substituents was obtained. The relationships were also used to estimate a value of K_b for sulfanilamide. This estimated value differed from the commonly accepted value, but showed close agreement with the new value (1.1×10^{-12}) obtained from spectrophotometric data. It is suggested that the high ρ value for uracil with respect to the benzene derivatives is additional evidence for the imidic type of dissociation in uracil.

Several recent studies have been concerned with the effect of sulfur-containing substituents upon the activity of various benzene derivatives such as benzoic acid, phenol and anilinium ion.[2-4] Since derivatives of uracil containing similar sulfur substituents were available to us from synthetic studies carried out in this Laboratory,[5,6] it seemed of interest to determine the ionization constants of these compounds and to compare the results with the data available from the benzene series.

The ionization constants of the three uracil derivatives, 6-uracilsulfonic acid (secondary ionization), 6-uracilsulfonamide and 6-uracil methyl sulfone, were determined by potentiometric titration at 25° and were corrected to approximate thermodynamic values in the usual manner.[7] It is at once apparent from the pK_a values collected in Table I that the sulfur-containing groups exert a profound effect upon the acidity of the uracil residue and that the order of increasing acidifying power $-SO_3^- \ll -SO_2NH_2 < -SO_2CH_3$ is in agreement with the results found in other series. The low acidifying power of the sulfonate groups has been ascribed to the presence of the formal negative charge and is also reflected in its reduced *meta*-directing property.[8a]

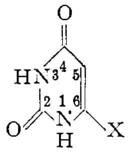
TABLE I

ACIDIC DISSOCIATION OF URACIL RESIDUES AT 25°

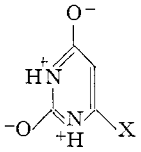
	pK_a	log K/K°	σ^a
Uracil[b]	9.45	...	...
6-Uracilsulfonic acid	7.26	2.19	0.52
6-Uracilsulfonamide	5.43	4.02	0.98
6-Uracil methyl sulfone	4.73	4.72	1.16

[a] Based on a ρ-value of 4.10 derived as indicated in the text. [b] P. A. Levene, L. W. Bass and H. S. Simms, *J. Biol. Chem.*, **70**, 229 (1926).

Any attempt to correlate the effect of these substituents in the 6-position of uracil with the effect produced in the benzene series is complicated by the question of whether to consider the proton as leaving from one of the nitrogen atoms of the lactam form A, or from one of the hydroxyl groups of the lactim form C hypothetically in equilibrium with it. Actually, however, the greater part of the evidence bearing on the structure of such lactams seems strongly to corroborate Arndt's zwitterionic lactam formulation (A ⟷ B) and would therefore suggest that "X" is structurally related to an *ortho* or *para* substituent in the benzene series rather than to a *meta* substituent.[9,10] In addition, it would seem more reasonable to make the comparison with substituents placed in the *para* rather than the *ortho* position of the benzene derivatives



A



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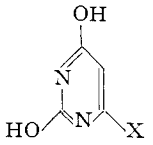

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[1] This work was supported by a grant from the American Cancer Society upon recommendation of the Committee on Growth of the National Research Council.

[2] F. G. Bordwell and G. D. Cooper, THIS JOURNAL, **74**, 1058 (1952).

[3] H. Zollinger, W. Büchler and C. Wittwer, *Helv. Chim. Acta*, **36**, 1171 (1953).

[4] R. D. McCoy and D. F. Swinehart, THIS JOURNAL, **76**, 4708 (1954).

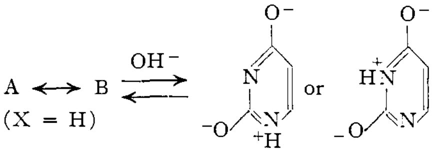
[5] S. B. Greenbaum and W. L. Holmes, *ibid.*, **76**, 2899 (1954).

[6] S. B. Greenbaum, *ibid.*, **76**, 6052 (1954).

[7] S. Glasstone, "Text-Book of Physical Chemistry," D. Van Nostrand Co., Inc., New York, N.Y., 1940, p. 963.

[8] C. K. Ingold, "Structure and Mechanism of Organic Chemistry," Cornell Univ. Press, Ithaca, N.Y., 1953, (a) p. 236, (b) p. 743, (c) p. 739.

[9] This view holds that the structure of uracil and related compounds is best expressed by a retention of the protons at both nitrogen atoms and by an indication of the considerable participation (*via* zwitterionic forms) of the six π-electrons in typical aromatic conjugation. The ionization is then expressed as a loss of a proton from one of the nitrogen atoms with the resulting formation of an anionic system indistinguishable from one that would be produced by the ionization of the hypothetical enol form.



F. Arndt, *Rev. faculté sci. univ. Istanbul*, **9A**, 19 (1944); F. Arndt, L. Loewe and L. Ergener, *ibid.*, **A13**, 103 (1948); F. Arndt in "Organic Analysis," Vol. I, Interscience Publishers Inc., New York, N.Y., 1953, p. 197 ff. For an excellent review of the physical aspects of the problem see D. O. Jordon, *Ann. Rev. Biochem.*, **21**, 209ff. (1952).

[10] The ultraviolet absorption data first presented by Shugar and Fox (*Biochim. Biophys. Acta.*, **9**, 199 (1952)) and later elaborated upon by Bergmann and Dikstein (THIS JOURNAL, **77**, 691 (1955)) are preponderantly in favor of an initial dissociation from the N_1-position. It is interesting to note, however, that although uracil reacts with diazomethane to afford a 3-methyl derivative exclusively, benzuracil initially affords a 3-methyl derivative (ref. 9).

since compounds like *o*-toluidine demonstrate a pronounced primary steric effect (*o*-toluidinium ion is a stronger acid than anilinium ion),[8b,11] while uracil does not (6-methyluracil is a weaker acid than uracil).[12]

The actual existence of a simple relationship between the relative acidifying effect of these substituents in the benzene series and the 6-uracil series was demonstrated by a plot of log K/K^0 for the *p*-sulfonates of benzoic acid, phenol, anilinium ion and the 6-sulfonate of uracil *vs.* the corresponding value of log K/K^0 for the respective methyl sulfones (Fig. 1) (K^0 is the ionization constant of the unsubstituted acid and K is the constant for the substituted compound). The values of K and K^0 for the benzene derivatives are given in Table III and represent what appeared to be the most carefully derived figures in each case. It is important to note that the straight line produced by these points does not pass through the origin as would be expected from the ideal Hammett equation, log $K/K^0 = \rho\sigma$ (1), where ρ and σ are defined independently of each other.[11] This type of deviation indicates that in the case of these derivatives σ is not independent of ρ, and that σ is probably the same function of ρ in both the benzene and uracil series.

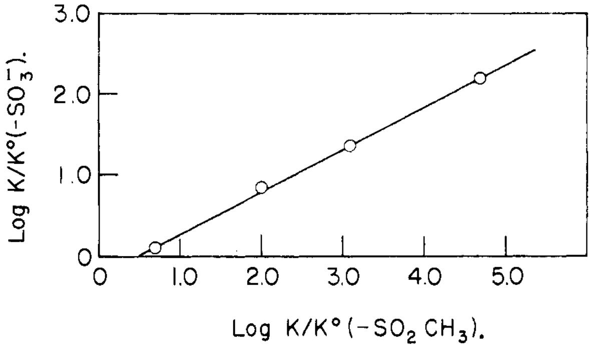


Fig. 1.—A comparison of the effect of the sulfonate and methylsulfonyl groups on the acidity of *para*-substituted benzene derivatives with their effect as substituents of the 6-position of uracil. The points in order of increasing magnitude are for the derivatives of benzoic acid, phenol, aniline and uracil, respectively.

In general, variations in σ have been shown to occur with strong electron withdrawing or donating groups and have been ascribed to interconjugation effects between the acidic group and the substituent group.[2,14] Thus with the electron-withdrawing groups, increasing values of σ are actually required when they are substituted in the benzoic acid systems, the thiophenol systems, and the aniline-phenol systems.[11-13] Despite this indication of a multiplicity of values of σ for a given substituent, the feeling has persisted that there are only two discrete values of σ for any substituent which can enter into such interconjugation, one for use with acidic groups which participate to a significant extent in this mesomeric interaction and one for use with acidic groups which do not.[13,14] For example, in reviewing the Hammett equation, Jaffé has found it convenient to introduce the single symbol σ^* for both the aniline and phenol systems since values in these two systems are usually of the same order of magnitude but are of a different order of magnitude from those found in the benzoic acid system.

TABLE II

ACIDIC DISSOCIATION OF BENZENE DERIVATIVES AT 25°

	pK_a	log K/K°	σ^a
Benzoic acid[b]	4.20	...	...
p-Sulfo-[c]	4.11	0.09	0.09
p-Methysulfonyl-[d]	3.48	0.72	0.72
Phenol	9.85	...	...
p-Sulfo-[c]	9.03	0.82	0.39
p-Methylsulfonyl-[f]	7.83	2.02	0.96
Aniline	4.58	...	...
p-Sulfo-[g]	3.23	1.35	0.49
p-Methylsulfonyl-[f]	1.48	3.10	1.11

[a] Based on the Jaffé ρ-values of 1.00, 2.11, 2.77 for benzoic acid, phenol and aniline, resp. [b] The figures for the unsubstituted acid are the retrogression intercept values of Jaffé (ref. 13). [c] Ref. 3. [d] Ref. 2, from σ-value given. [e] E. E. Sager, M. R. Schooley, A. S. Carr and S. F. Acree, *J. Research Natl. Bur. Standards*, **35**, 521 (1945). [f] Ref. 2. [g] R. O. MacLaren and D. F. Swinehart, THIS JOURNAL, **73**, 1822 (1951).

Since the data found in Fig. 1 indicate that σ is dependent on ρ, it was necessary to allow for this in deriving the ρ-value for the uracil derivatives. The simplest straight-line relationship involving σ and ρ which approximates the data at hand is found in a plot of log K/K^0 against ρ. A plot of this type for the sulfonates of the three benzene derivatives is given by the lowest three points of curve A,

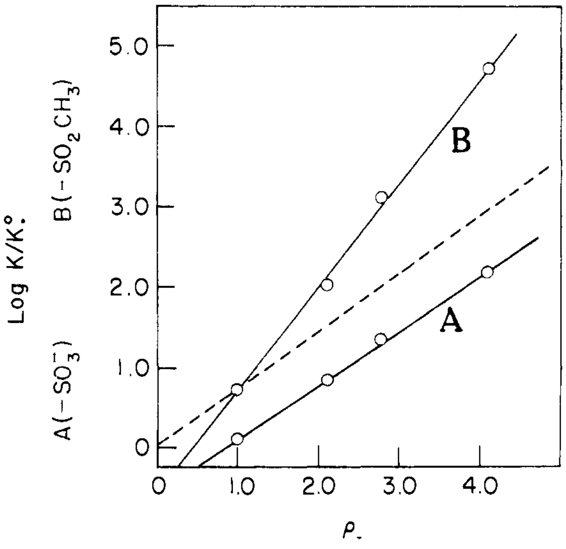


Fig. 2.—The points in order of increasing ρ-value are for the *para*-substituted derivatives of benzoic acid, phenol and aniline, and the 6-substituted derivatives of uracil. The ρ-value for uracil was obtained by extrapolating one curve to log $K/K°$ for the uracil derivative and this value of ρ was utilized in constructing the second curve. The dashed line represents the ideal "Hammett" equation for the methyl sulfones.

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(11) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N.Y., 1940, Chap. VII.

(12) J. R. Marshall and J. Walker, *J. Chem. Soc.*, 1013 (1951).

(13) H. H. Jaffé, *Chem. Revs.*, **53**, 191 (1953).

(14) G. E. K. Branch and M. Calvin, "The Theory of Organic Chemistry," Prentice-Hall, Inc., New York, N.Y., 1945, p. 257.

Fig. 2. By extrapolating to the experimental value of log K/K^0 for the uracil derivative a fourth point corresponding to a ρ-value of 4.10 for the uracil compound is obtained. If this value of ρ is now applied to the uracil compound in a similar plot involving log K/K^0 for the four methyl sulfones, a reasonable straight-line relationship is produced again (Fig. 2, curve B). (It might be noted that the intercept $\rho = 0$ has a negative value in both these cases.) If it is assumed that ρ actually is a constant for a given ionizing system and that the σ-value for the substituent is a quantity that varies from system to system, then the equations representing the curves of Fig. 2 may be put in the form

$$\log K/K^\circ = m\rho + A, \text{ from whence} \quad (2)$$

$$\sigma = m + A/\rho, \text{ and} \quad (3)$$

$$d\sigma/d\rho = -A/\rho^2 \quad (4)$$

where m is the slope and A is the intercept $\rho = 0$. These equations imply that in the case of these derivatives there is an inherent multiplicity greater than two for the value of σ (*i.e.*, σ varies with ρ). They also indicate, however, that the variation of σ with ρ decreases rapidly with increasing values of ρ, and that eventually this variation is quite small. Thus, the value of $d\sigma/d\rho$ for the sulfonic acid derivatives turns out to be 0.35 in the benzoic acid region but only 0.08 in the aniline region and 0.05 at the assigned ρ-value of uracil.[15,16]

The data in Table I provide a value of 4.02 for log K/K^0 for 6-uracilsulfonamide. On the assumption that the above equations also hold for the closely related sulfonamido group, a similar graph may be constructed using as the coördinates of the second point a ρ-value of 1 and a log K/K^0 value of 0.621. The latter come from Jaffé's value of σ for this substituent in compounds where there is little interconjugation with the acidic group.[16] By means of this graph a value of 2.60 may be estimated for log K/K^0 for the anilinium dissociation of sulfanilamide, a compound in which the amino group can participate in such resonance interaction. This value and the corresponding K_b value of 0.96×10^{-12} do not agree very well with values derived from the data found in the literature and they are in greatest disagreement with the commonly accepted value of Bell and Roblin (Table III). Since the reported constants were derived from potentiometric titrations involving *p*H ranges where the Henderson equation is difficult to apply,[7] the dissociation constant was redetermined by ultraviolet absorption spectroscopy. The latter method permits a more direct measurement of the concentration of the species involved,[17] and is particularly suited to a compound like sulfanilamide where the spectrum is uncomplicated and demonstrates a large hyperchromic shift as the amino group is changed from its acid to basic form.[18] The values of K_b and σ obtained by this method (Table III) were found to be in much better agreement with the graphically estimated values. The plot of log K/K^0 *vs.* ρ for the sulfonamides is shown in Fig. 3.

TABLE III

BASIC DISSOCIATION OF SULFANILAMIDE

	$K_b \times 10^{12}$	log $K/K^{\circ a}$	σ
Bell and Roblin[b]	2.3	2.22	0.80
Albert and Goldacre[c]	1.6	2.38	.86
This work (measd.)	1.1	2.53	.92
Estimated value	0.96	2.60	.94

[a] Calculated as anilinium ion dissociation. [b] P. H. Bell and R. O. Roblin, Jr., THIS JOURNAL, **64**, 2905 (1942). [c] A. Albert and R. Goldacre, *Nature*, **149**, 245 (1942).

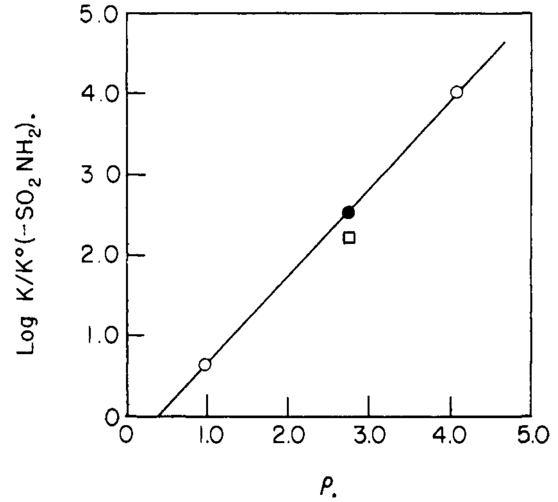

Fig. 3.—Equation 2 applied to the sulfonamido derivatives. The open circles correspond, respectively, to Jaffé's value of σ in compounds paralleling the benzoic acid system (ρ 1.00) and to the data for 6-uracilsulfonamide (ρ 4.10). The experimental values for the ionization of the 4-amino group of sulfanilamide are given by ● (this work) and □ (Bell and Roblin).

Conclusions from this work must be drawn cautiously because of the limited nature of the compounds studied and in view of the several assumptions made in developing the relationships. It seems worthwhile, nevertheless, to call attention to certain inferences present in the results. The apparent high ρ-value for uracil as compared to the values for phenol and aniline may possibly be considered an indication of a shortening of the distance between the ring and the acidic group. Thus, the ρ-values of cinnamic and benzoic acids are 0.466 and 1.00, of benzoic acid and phenol are 1.00 and 2.11, of anilinium and pyridinium ions

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(15) If σ_0 is defined as σ for benzoic acid ($\rho = 1$) then equation 3 may be put in the form (5) $\log K/K^\circ = [\sigma_0 + A(1 - \rho)/\rho]\rho$ and this is obviously a special case of a more generalized relationship, also proposed by Hammett: (6) $\log K/K^\circ = [\sigma + \sigma' f(\rho)]\rho$ (ref. 13, p. 231).

(16) These equations are not meant to imply that all aromatic acid systems substituted with these sulfur groups should follow the deviation pattern found in Figs. 1 and 2, since in systems where there is little conjugation between the substituent group and the actual proton-releasing group (*e.g.*, the –OH group of the carboxylic acid) the ideal Hammett equation is followed quite well. For example, the ρ-values of the phenylboric, carboxylic, arsonic and phosphonic acids have been correlated with the polarizability of the "central atom" (the B, C, P, etc.) as calculated from ionic refractivities (H. H. Jaffé, L. D. Freedman and G. O. Doak, THIS JOURNAL, **75**, 2209 (1953)) and the σ-values for these acids are reasonably independent of ρ. They are simply represented on the deviation curve by the point for benzoic acid where ρ has been defined as 1.

(17) L. A. Flexser, L. P. Hammett and A. Dingwall, THIS JOURNAL, **57**, 2103 (1935).

(18) J. M. Vanderbelt and L. Doub, *ibid.*, **66**, 1633 (1944).

are 2.77 and 3.15, respectively.[19] In each of these cases the larger value is associated with a decrease in this distance.[8c] On such a basis, the data would seem to present additional cogent evidence for the imidic type of dissociation in uracil (where the acidic group is now a part of the ring (A ⟷ B)) rather than the enolic type of dissociation (where the acidic group is exocyclic C.)[9] The additional possibility that although the original comparison was made with *p*-substituted benzene derivatives, we actually are dealing (in the case of the 6-uracil derivatives) with dissociation from the nitrogen proximal to the substituent group and that the increased effect of the substituent is related in part to added short-range or inductive effects still leads to the same conclusion favoring imidic dissociation. (The acidifying power of these substituents is lowered by placing them in an intermediate, *i.e.*, *meta* position in the benzene series.[2-4])

The curves in Figs. 2 and 3 indicate that in certain cases a relatively simple dependence of σ on ρ can be demonstrated and that the dependence appears to be of a limiting type involving a term such as A/ρ.[20] The ubiquitous similarity of the σ values for phenol and aniline may stem, therefore, from the fact that the ρ-values for these two systems lie close together and are of a relatively high order of magnitude.

Acknowledgment.—The author wishes to express his appreciation to Professor Arnold D. Welch for his continued interest in the investigation of these derivatives of uracil and to Professor Fritz Arndt for several conversations concerning the structure of uracil and related compounds.

Experimental

(a) The 6-uracilsulfonic acid, sulfonamide and methyl sulfone were analytical samples prepared as previously described.[5,6] Five-ml. aliquots of 0.005 *M* solutions were titrated with 0.1 *N* carbonate-free sodium hydroxide by means of a 500-μl. "Micrometric" buret assembly and a Beckman *p*H meter. The temperature was maintained at 25 ± 1°. Readings were taken after the addition of every 10 μl. of titrant except at the critical regions where the readings were taken after the addition of every 5 μl. The pK_a was determined from three points on the curve for which approximate thermodynamic corrections were calculated by means of the Debye–Hückel equation. The final values are given in Table I.

(b) The basic dissociation of sulfanilamide was determined by ultraviolet absorption spectroscopy. A stock solution was prepared by dissolving 39.79 mg. of triply recrystallized sulfanilamide (Merck and Co., Inc.) in 500 ml. of water. Ten ml. of the stock solution and the appropriate quantity of carefully prepared 0.1 *N* hydrochloric acid were used to prepare 100-ml. portions which were 0, 0.005, 0.01 and 0.02 *N* with respect to the acid. A solution which was 2 *N* with respect to acid also was prepared. Blanks were prepared for each type of solution by the omission of the sulfanilamide. The *p*H of the dilute acid solutions were determined at 25° with the *p*H meter and these values were checked against values calculated from the "International Critical Tables." The solutions (still maintained at 25°) were transferred quickly to a Beckman model DU spectrophotometer equipped with a water-cooled cell compartment and the absorption at 275 mμ was then determined. (The measured temperature variations were less than 1° by this procedure.) A Beer's law check was made at the given wave length and from the intercept the cell correction of +0.004 was obtained. The data are given in Table IV.

TABLE IV

DETERMINATION OF pK_a OF 4-AMINO GROUP OF SULFANILAMIDE, concentration, 7.96 mg./l.

Buffer, *N* HCl	*p*H[a]	*D* (275 mμ)	log BH$^+$/B	log fBH$^+$/fB	pK_a
0.005	2.34	0.250	−0.26	−0.04	2.04
.010	2.03	.185	+ .07	− .05	2.05
.020	1.74	.125	+ .38	− .07	2.05

D (275 mμ) 0.377 in H_2O, 0.020 in 2 *N* HCl, pK_a (av.) 2.05, K_b 1.12×10^{-12}. [a] *p*H of 0.005, 0.010, 0.020 *N* HCl solutions calcd., 2.33, 2.04, 1.75, respectively. ("International Critical Tables," McGraw–Hill Book Co., Inc., New York, N. Y., 1930, Vol. VII, p. 233.)

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[19] The "acidic group" refers to the actual proton releasing group, *i.e.*, the –OH group of the carboxylic acid. The values are from ref. 13 except for the estimation of pyridine which was calculated from the values of pK_a for pyridine (5.23) (A. Gero and J. J. Markham, *J. Org. Chem.*, **16**, 1835 (1951)) and 4-pyridine methyl sulfone (1.74) (S. Greenbaum, to be published).

[20] Any relationship between σ and ρ obviously must require reference to a common solvent system.

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF THE GENERAL ELECTRIC CO.]

Cyanomethyl Silicon Compounds

BY MAURICE PROBER

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Cyanomethyltrimethylsilane, cyanomethylpentamethyldisiloxane and cyanomethylheptamethylcyclotetrasiloxane were prepared by treating the chloromethyl Grignard reagents with cyanogen. Iodomethyltrimethylsilane was cleaved by silver cyanide. The hydrolytic behavior and equilibration of these nitriles is discussed. The physical properties of the compounds indicate increased intermolecular forces.

It has long been felt that the properties of siloxanes would be altered significantly by introducing polar groups into the hydrocarbon portion of the siloxane chain. The nitrile group is one of the very polar functional groups, and the preparation of cyanomethyl silicon compounds was one of the objectives of a program on carbon-functional silicon compounds undertaken in this Laboratory. Cyanomethyl silicon compounds hitherto have not been prepared, and very few nitrile containing carbon-functional silicon compounds have been reported.[1]

The compounds selected for study were cyanomethyltrimethylsilane (I), cyanomethylpentamethyldisiloxane (II) and cyanomethylheptamethylcyclotetrasiloxane (III).

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[1] L. H. Sommer and J. Rockett, THIS JOURNAL, **73**, 5310 (1951); D. W. Lewis and G. C. Gainer, *ibid.*, **74**, 2931 (1952); D. Speck, *J. Org. Chem.*, **18**, 1689 (1953); L. H. Sommer, G. M. Goldberg, G. H. Barnes and L. S. Stone, Jr., THIS JOURNAL, **76**, 1609 (1954).