

somewhat stronger bands at 2560 cm^{-1} (mercapto group) and 1440 cm^{-1} (carbomethoxy group).

Dimethyl 11,11'-dithiodiundecanoate. When the ethanol solution from the iodine titration of methyl 11-mercapto-undecanoate was cooled to 0°, a crystalline precipitate formed. This solid crystallized from petroleum ether as transparent plates, m.p. 56°.

Anal. Calcd. for $\text{C}_{24}\text{H}_{46}\text{O}_4\text{S}_2$: C, 62.3; H, 10.0; S, 13.9. Found: C, 62.7; H, 10.1; S, 13.7.

Analytical and physical data. The mercapto compounds described in this paper were analyzed by titration with 0.1*N* iodine in ethanol. Water was added during the titration in case of slow decolorization as the end point was approached.

With mercapto acids, the sample was first titrated in ethanol with 0.1*N* aqueous sodium hydroxide to the phenolphthalein end point. Following this determination of the carboxyl group, the pink color was just discharged with a few drops of 0.1*N* hydrochloric acid and the solution was then titrated with 0.1*N* iodine in ethanol to a faint permanent yellow color. The solution was titrated once again with 0.1*N* sodium hydroxide solution until the yellow color began to turn pink. The latter titration measured hydriodic acid liberated by the reaction of iodine with the mercapto

group, and checked on possible impurities that merely absorbed iodine. With pure mercapto acids analysis showed equivalent amounts of carboxyl and mercapto groups and liberated hydriodic acid.

Infrared absorption spectra were obtained on thin liquid films or on carbon disulfide solutions with a Perkin-Elmer Model 21 spectrophotometer, using sodium chloride optics. In a few instances, solid compounds were examined as pressed potassium bromide disks or as nujol mulls. Ultraviolet absorption spectra were recorded on methanol solutions with a Carey Model 11 recording spectrophotometer.

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Some α -Carbalkoxyalkoxysilanes

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Several α -carbalkoxyalkoxysilanes were prepared by the reaction of ethyl lactate or methyl α -hydroxyisobutyrate with a methyl- or phenylchlorosilane in the presence of a tertiary amine, or by interchange with the corresponding ethoxysilane. When these substances react with glycols, either the ester bond or the silicon-oxygen bond may be attacked. This competition was studied, particularly as affected by the structure of the reactants.

Alkoxysilanes derived from alcohols containing a second functional group are of interest because they offer an opportunity to carry out subsequent reactions with relative ease and thereby to arrive at new organo-silicon compounds. Among representatives of these classes of compounds, only the β -halogenoalkoxysilanes¹ and the β -alkoxyalkoxysilanes² are as yet reasonably well known. Recently Henglein and coworkers³ described trimethylsiloxy derivatives of lactic and tartaric acids and their ethyl esters.

α -Carbalkoxyalkoxysilanes can be prepared readily from the appropriate chlorosilane and an α -hydroxy ester in the presence of a tertiary amine; or they can be prepared from the corresponding methoxy- or ethoxysilane in the presence of an ester interchange catalyst. The former method, due

to Martin⁴ was discussed at some length by the present author and L. S. Nelson.⁵ α -Carbalkoxyalkoxysilanes based on ethyl lactate or methyl α -hydroxyisobutyrate as the alkoxy component and methyl- or phenylchlorosilanes as the organo-silicon component were prepared and their subsequent reaction with a diol or a dibasic acid were studied.

The α -carbalkoxyalkoxysilanes prepared are di- and triesters, and should be convertible to polymeric esters by normal reesterification procedures. However, a competing reaction is always possible—a reaction that is formally the reverse of that by which the ester was prepared. A diol can attack such a molecule either at the terminal ester function or at the interior silicon-oxygen bond. The first mode of attack produces a poly(siloxy ester); the second liberates the hydroxy ester and produces a poly(alkylenesilane) instead. These relations are shown, in the case of a difunctional reactant, in the following scheme.

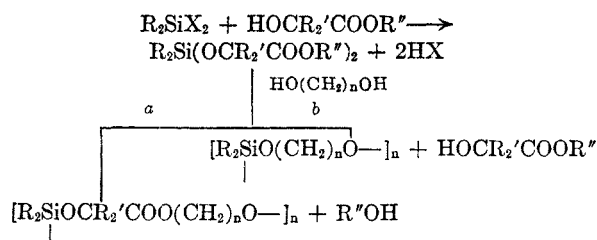
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For a trifunctional silane route *a* leads to a cross-linked carbalkoxyalkoxysilane polymer, while route *b* leads to a cross-linked alkoxysilane polymer, devoid of the carbalkoxy component. Some factors that affect the course of the reaction were studied. These include the structure of the organo-silicon component, that of the hydroxy ester, and that of the diol; the choice of catalyst and of experimental conditions. It was found that the polyesterification reaction is favored over attack at the silicon-oxygen bond when the silicon atom bears three rather than two methyl or phenyl substituents, when the substituents are phenyl rather than methyl, when the α -carbon atom in the ester bears two methyl substituents rather than one, and when the glycol used is of relatively short chain length. There are some exceptions to these generalizations. A somewhat surprising result was that a highly branched glycol (pinacol) reacted almost exclusively at the Si-O bond to produce a five-membered-ring alkylene dioxysilane. A second rather unexpected observation was that some dephenylation occurred during reactions involving bis(α -carbalkoxyalkoxy)diphenylsilanes. Gelation occurred in the course of these reactions, and a small amount of benzene was found among the volatile products.

Carbalkoxy substituted alkoxysilanes might be useful as components of polyester type resins. When the initial functionality is greater than 2, these resins normally contain free hydroxyl groups, free carboxyl groups, or both. It was therefore of some interest to investigate the reaction of polybasic acids as well as that of diols, and succinic acid was chosen as a typical representative. This reagent always attacked the silicon-oxygen bond, liberated the α -hydroxy ester and formed a poly(acyloxysilane) or its thermal decomposition products.

EXPERIMENTAL

Preparation of α -carbalkoxyalkoxysilanes from chlorosilanes and α -hydroxy esters (Method A). The preparation of bis(α -carbomethoxyethoxy)diphenylsilane serves to illustrate this method of preparation. A solution of 236 g. (2 moles) of ethyl lactate (Distillation Products, White Label) in 174.2 g. (2.2 moles) of reagent grade pyridine was stirred mechanically and cooled in an ice bath to 5°. Redistilled diphenyldichlorosilane (253 g., 1 mole) was added dropwise during 45 min. The temperature was not allowed to rise above 35°. A very heavy precipitate of pyridine hydrochloride was formed. Rapid stirring was maintained, and at the end of the addition of the chlorosilane 300 ml. of dry ether was added to loosen this precipitate. The salt was

rapidly filtered on a coarse sintered glass funnel and washed several times with dry ether. The filtrate and washings were combined, refiltered through fluted paper, and concentrated at atmospheric pressure until the vapor temperature reached 75°. The pressure was then reduced and the remaining solvents and low boiling by-products were removed as the pressure was gradually reduced from 80 mm. to 1.5 mm. The major product (293 g., 70% yield) then distilled over at 180–197°/1.0–1.5 mm. Redistillation gave 262.5 g., b.p. 193–5°/1.5 mm., n_D^{20} 1.5098. A somewhat purer sample had the constants shown in Table I.

Preparation of α -carbalkoxyalkoxysilanes from ethoxysilanes and α -hydroxy esters (Method B). The preparation of methyltris(α -carbomethoxy- α -methylethoxy)silane will serve as an illustration. One mole (178 g.) of purified methyltriethoxysilane, 389.4 g. (3.3 moles) of methyl α -hydroxy isobutyrate (Distillation Products, Practical Grade), and 3.6 g. of (+)-camphorsulfonic acid were stirred and heated under a 12" Vigreux column. Ethanol began to distill over when the temperature reached 125°. The reaction was, however, very sluggish. After 13 hr. at 120–160°, 142 g. of impure ethanol (containing some unreacted methyltriethoxysilane) was collected. Unreacted methyl α -hydroxy isobutyrate and triethoxysilane (160 ml., b.p. 110–137°) were removed by distillation and the residue was fractionated under vacuum. After a small fore-run, an intermediate fraction (84.5 g., b.p. 140–145°/10 mm., n_D^{20} 1.4229) that appeared to be the partially reacted product, bis(α -carbomethoxy- α -methylethoxy)ethoxymethylsilane was obtained. (Sapon. equiv.: Calcd. for $C_{12}H_{26}SiO_7$, 161.2; found, 157.1). The completely reacted product (118 g.) boiled at 172–174°/10 mm., n_D^{20} 1.4312–1.4319. (Sapon. equiv.: Calcd., 131.5; found, 133.8–134.4).

Yields, properties, and analytical data are summarized in Table I.

Reaction with diols. The carbalkoxyalkoxysilane was heated with an equivalent weight of the glycol in a small reaction flask to which a small Vigreux column and water-cooled condenser were attached. Usually either 0.1 or 0.2 mole of the carbalkoxyalkoxysilane was used, and 0.2–0.5 g. of sodium methylate or lead acetate was added to catalyze the reaction. Volatile reaction products were collected and identified by physical constants (boiling point, refractive index, and density). The resinous reaction products varied from viscous oils to gelled solids. These results are summarized in Table II.

Polymeric reaction products were obtained in all cases except that involving bis(α -carbomethoxyethoxy)-dimethylsilane and pinacol, where the products were ethyl lactate and dimethyl(tetramethylethylenedioxy)silane. The two volatile products appeared as an azeotrope that was not resolved (observed b.p. 148–149°, n_D^{20} 1.4185–1.4188). For identification, the previously unknown cyclic alkylenedioxy-silane was prepared from dimethyldiethoxysilane and pinacol. It has b.p. 153°, n_D^{20} 1.4170. The boiling point and molecular weight showed that the cyclic monomer was formed, rather than the dimer, as in some similar cases.⁵

Anal. Calcd. for $C_8H_{18}SiO_2$: C, 55.1; H, 10.4; mol. wt., 174.3. Found: C, 55.4; H, 10.8; mol. wt., 164 (in benzene).

Reaction with succinic acid. Either 0.1 or 0.2 mole of the α -carbalkoxyalkoxysilane was heated directly with an equivalent quantity of succinic acid in the type of apparatus described above and volatile products were again collected and identified. These results are also summarized in Table II.

The reaction of succinic acid (0.2 mole) with bis(α -carbomethoxy- α -methylethoxy)dimethylsilane (0.2 mole) is illustrative of one in which essentially complete formation of low-molecular weight products was observed, in accordance with the equation,

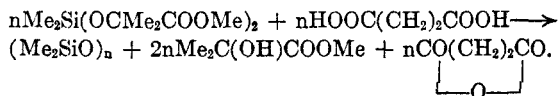
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TABLE I
 α -CARRBAKOKXYALKOKXYSILANES
 $R_nSi(OR')_m$

$n = 2,$ R	$m = 2$ R'	Yield, %	B.P., °C.	mm.	n_D^{20}	d_4^{20}	Analyses						Formula				
							C, % Calcd. Found	H, % Calcd. Found	Si, % Calcd. Found	NRp Calcd. Found	Sapon. Equiv. Calcd. Found						
CH ₃	CH ₃ CHCOOC ₂ H ₅	84	111-114	2.0	1.4211	0.864	49.3	48.8	8.3	8.7	9.6	10.2	72.5	71.8	146.2	150.5	C ₁₂ H ₂₄ SiO ₆
CH ₃	(CH ₃) ₂ CCOOC ₂ H ₅	66	131-133	18.0	1.4260	1.052	49.3	49.4	8.3	8.5	9.6	9.8	72.5	71.2	146.2	145.5	C ₁₂ H ₂₄ SiO ₆
C ₆ H ₅	CH ₃ CHCOOC ₂ H ₅	70	195-197	1.4	1.5106	—	63.4	63.0	6.8	6.9	6.7	6.7	—	—	—	—	C ₂₂ H ₃₈ SiO ₆
$n = 1,$ R	$m = 3$ R'																
CH ₃	CH ₃ CHCOOC ₂ H ₅	36 48	155-158 155-157	2.0 2.0	1.4255 1.4258	1.103 1.103	48.8 48.8	48.9 48.6	7.8 7.8	8.0 8.1	7.1 7.1	7.3 7.3	93.7 93.7	91.8 91.8	131.5 131.5	131.9 131.3	C ₁₆ H ₃₀ SiO ₉ C ₁₆ H ₃₀ SiO ₉
CH ₃	(CH ₃) ₂ CCOOC ₂ H ₅	33	171-174	10.0	1.4315	1.103	48.8	49.1	7.8	8.1	7.1	7.5	93.7	92.8	131.5	134.1	C ₁₆ H ₃₀ SiO ₉
C ₆ H ₅	CH ₃ CHCOOC ₂ H ₅	63	192-196	1.2-2.0	1.4664	—	55.3	55.2	7.1	7.1	6.1	6.2	—	—	—	—	C ₂₁ H ₃₂ SiO ₉
C ₆ H ₅	(CH ₃) ₂ CCOOC ₂ H ₅	64	179-180	1.0	1.4744	—	55.3	55.2	7.1	7.5	6.1	6.1	—	—	—	—	C ₂₁ H ₃₂ SiO ₉

TABLE II
REACTIONS OF ALKYL- α -CARBALKOXYALKOXYLSILANES, $R_nSi(OR')_m$

$\frac{n=2,}{R}$	$\frac{m=2}{R'}$	Reactant	Catalyst	Reaction Temp., °C.	Volatile Product	Approx. % Yield	Other Products	Approx. % Yield	Remarks
CH_3	$CH_3CHCOOC_2H_5$	Ethylene glycol	$NaOCH_3$	165-240	Ethyl lactate	100	—	—	—
			$Pb(OAc)_2$	165-265	{ Ethanol Ethyl lactate	50	—	—	—
		Pinacol	$NaOCH_3$	145-260	{ Ethyl lactate Hexamethylethylene- dioxysilane	70	—	—	—
			$Pb(OAc)_2$	136-190	{ Ethyl lactate Hexamethylethylene- dioxysilane	65	—	—	—
		Succinic acid	None	196-268	Ethyl lactate	85	—	—	—
						100	Succinic anhydride Dimethylsiloxane	100	—
CH_3	$(CH_3)_2C-COOC_2H_5$	Ethylene glycol	$Pb(OAc)_2$	135-206	Methanol	100	Sirupy liquid polymer	100	—
		Succinic acid	None	170-220	Methyl isobutyrate	90	Succinic anhydride Dimethylsiloxane	100	—
CaH_5	$CH_3CHCOOC_2H_5$	Ethylene glycol	$Pb(OAc)_2$	150-250	Ethanol	95	Alkoxy silane polymer	100	Gelled at ~95% re- action
		Trimethylene glycol	$Pb(OAc)_2$	157-209	{ Ethanol Ethyl lactate	65	—	—	Incipient gellation
		Pentamethylene glycol	$Pb(OAc)_2$	160-280	{ Benzene Ethanol	5	—	—	—
		2,4-Dimethyl-2-ethoxy- methylpentane-1,5- diol	$Pb(OAc)_2$	195-218	{ Ethyl lactate Benzene	75	—	—	Insoluble gel formed
					{ Ethanol Ethyl lactate	10	Heavy, viscous oil	—	—
						10	—	—	—
						90	—	—	—
$\frac{n=1,}{R}$	$\frac{m=3}{R'}$								
CH_3	$CH_3CHCOOC_2H_5$	Ethylene glycol	$Pb(OAc)_2$	151-216	Ethanol	75	—	—	Incipient gellation at 75% reaction
		Pinacol	$Pb(OAc)_2$	161-200	{ Ethanol Ethyl lactate	70	Sirupy resin	—	—
		Succinic acid	None	184-247	Ethyl lactate	45	—	—	Gelled at 45% reac- tion
CH_3	$(CH_3)_2C-COOC_2H_5$	Ethylene glycol	$Pb(OAc)_2$	156-200	Methyl isobutyrate	35	Heavy, yellowish liquid	—	—
					Methanol	5	—	—	—
CaH_6	$CH_3CHCOOC_2H_5$	Ethylene glycol	$Pb(OAc)_2$	143-175	Ethanol	70	—	—	Incipient gellation at 70% reaction
CaH_6	$(CH_3)_2C-COOC_2H_5$	Ethylene glycol	$Pb(OAc)_2$	145-190	Methanol	75	—	—	Incipient gellation at 75% reaction



Methyl α -hydroxyisobutyrate (b.p. 136–17°, n_D^{20} 1.4107–1.4111) was collected in over 90% yield. The non-volatile product (a pasty solid) was digested with two 50 ml. portions of cold *n*-hexane. The insoluble portion (19.8 g., 99% of the theoretical yield) was succinic anhydride [microscopic needles that sublime readily above 100°, m.p. 116° (uncorr.)

after crystallization from benzene or toluene]. The *n*-hexane solution was concentrated, filtered from a little more succinic anhydride, and then the remaining solvent was distilled. The limpid oil that remained (12.6 g., 85% of the theoretical amount) was identified as an impure mixture of dimethylsiloxane polymers by refractive index and viscosity characteristics.

Similarly, with bis(α -carbethoxyethoxy)dimethylsilane, nearly quantitative yields of ethyl lactate, succinic anhydride, and polydimethylsiloxane were obtained.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND THE LABORATORY OF PHARMACEUTICAL CHEMISTRY OF THE UNIVERSITY OF NEW MEXICO]

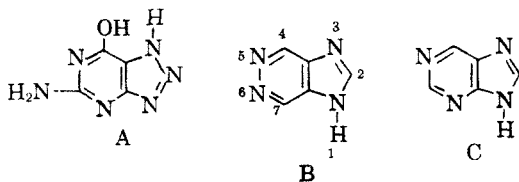
Imidazo[4,5-*d*]pyridazines. I. Synthesis of 4,7-Disubstituted Derivatives¹

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Eleven new imidazo[4,5-*d*]pyridazines were prepared. These include the 4,7-disubstituted compounds: dichloro, monochloromonohydroxy-, diamino-, dimercapto-, and various substituted mercaptans. The adenine analog, 4-aminoimidazo[4,5-*d*]pyridazine has been prepared. In addition, methyl 4(5)-imidazolecarboxylate-5(4)-phenylhydrazide and imidazole-4,5-dicarboxylic acid bismethylhydrazide were prepared. Attempts to prepare 4,5-diamino-3-pyridazone resulted in mixtures of 5-amino-4-chloro-3-pyridazone and 4-amino-5-chloro-3-pyridazone.

The antitumor activity of 8-azaguanine (5-amino-7-hydroxy-*v*-triazolo[*d*]pyrimidine), A³, encouraged the present authors to prepare the imidazo[4,5-*d*]pyridazine ring system, B, in which the two nitrogen atoms are adjacent in the six-membered ring with the five-membered imidazole ring remaining the same as in the parent purine ring, C. The work of Robins *et al.*⁴ has resulted in additional active compounds.



After 4,7-dihydroxyimidazo[4,5-*d*]pyridazine, IV, was prepared, the work of Baker,⁵ Jones,⁶ Gardner, *et al.*,⁷ came to our attention. Compound IV is the only imidazo[4,5-*d*]pyridazine reported here that

has been previously described. 4,7-Dichloroimidazo[4,5-*d*]pyridazine, V, was obtained only in low yield by treatment of IV with phosphorus oxychloride in dimethylaniline. Attempts to prepare compound V under a variety of other chlorinating conditions were unsuccessful. Very small amounts of 4(7)-chloro-7(4)-hydroxyimidazo[4,5-*d*]pyridazine, Va, were sometimes obtained.

In view of the difficulties in obtaining V it appeared desirable to obtain 4,7-diaminoimidazo[4,5-*d*]pyridazine from the 4,7-bismethylmercaptoimidazo[4,5-*d*]pyridazine. Compound VII was obtained from 4,7-dimercaptoimidazo[4,5-*d*]pyridazine, VI, by methylation in alkali. Compound VI was obtained from compound IV by thiation with phosphorus pentasulfide in dry pyridine in good yield. When compound VI was treated with one mole of methyl iodide in alkaline solution 4(7)-methylmercapto-7(4)-mercaptoimidazo[4,5-*d*]pyridazine, IX, was obtained in good yield. Compound IX when dethiated with Raney nickel gave 4-methylmercaptoimidazo[4,5-*d*]pyridazine, X. Compound X was converted to the adenine analog, 4-aminoimidazo[4,5-*d*]pyridazine, XXIV, with ethanolic ammonia in a bomb at 200°. 4(7)-Ethylmercapto-7(4)-mercaptoimidazo[4,5-*d*]pyridazine, XI, was obtained from VI by treatment with equal molar proportions of ethyl iodide in alkaline solution. However, when VI was treated with excess ethyl iodide in limited alkaline solution 4,7-bisethylmercapto-1-ethylimidazo[4,5-*d*]pyridazine hydrogen iodide, XII, was obtained. Compound XII upon treatment with sodium hydroxide solution produced the free base, XIII.

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(2) In partial fulfillment of the requirements of the Master of Science degree in chemistry at the University of New Mexico.

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