Short Title:

I. SILYL ORGANOMETALLIC COMPOUNDS
II. STRUCTURE OF GOMATINE

PART I: REACTIONS OF SOME SILYL ORGANOMETALLIC COMPOUNDS

PART II: ELUCIDATION OF THE STRUCTURE OF GOMATINE, A COMPOUND HAVING ANTIHISTAMINIC ACTIVITY, EXTRACTED FROM CROWN GALL TUMORS OF TOMATO PLANTS

by

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Part I: Reactions of Some Silyl Organometallic Compounds

Abstract

The reactions of some silyl organometallic compounds with acid chlorides, anhydrides, aldehydes, and ketones were investigated. Trimethylsilylmethylmagnesium chloride reacted with aromatic and aliphatic acid chlorides to give the corresponding methyl ketones. In the same way, the reaction of trimethylsilylphenylmethyllithium with benzoyl chloride yielded desoxybenzoin. Trimethylsilylmethylmagnesium chloride reacted with phthalic anhydride to give a di-γ-lactone, but did not react with aliphatic anhydrides to give any identifiable products.

Aromatic aldehydes and ketones were reduced to the corresponding pinacols by reaction with chlorotrimethylsilane and magnesium in hexamethylphosphoramide. Benzophenone, however, yielded p-benzoyltriphenylmethane and not benzopinacol. Aliphatic ketones did not undergo this pinacolic reduction under the same conditions.

Part II: Elucidation of the Structure of Gomatine, a Compound Having Antihistaminic Activity, Extracted from Crown Gall Tumors of Tomato Plants

Abstract

Gomatine, a compound having antihistaminic activity, isolated from crown gall tumor extracts of tomato plants by Kovacs and Wakkary, was not a pure compound, but seemed to be a mixture of at least two substances: one had the structure of tomatine with an extra hydroxy group attached at any of several positions; the other had the structure of tomatine with a keto group at one of a number of positions. Gomatine was contaminated with tomatine quite often, and it could possibly have been contaminated with a glycoalkaloid of solasodine as well.

To my parents

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Preface to Experimental

Unless otherwise mentioned, all nuclear magnetic resonance spectra were recorded on 60-MHz instruments manufactured by Varian (T-60 and A-60). Those spectra that were run at 100 MHz, as mentioned in the experimental section, were recorded on a Varian HA-100 NMR spectrometer. Tetramethylsilane was generally used as either an external or internal standard.

The infrared spectra were recorded on either a Perkin-Elmer grating spectrophotometer model 257 or model 337 unless otherwise specified.

Mass Spectra were measured on an AEI instrument, number MS902.

The ultraviolet spectra were recorded on a Unicam SP800 spectrophotometer.

The vapour phase chromatograms were recorded by an F & M Scientific 5750 Research Chromatogram, and a Perkin-Elmer Printing Integrator model 194 B was used to integrate the area under each peak.

Microanalyses were carried out by Microanalytic Laboratories, Denmark, and Organic Microanalyses, Montreal.

PART I

REACTIONS OF SOME SILYL ORGANOMETALLIC COMPOUNDS

INTRODUCTION

Carbon and silicon are both members of Group IV of the periodic table and have similar configurations of outer electrons. Although we may expect a degree of resemblance in the chemistry of these elements, they differ in the size of their atoms, their electronegativities, and the energies of their outer shell electrons. In particular the chemistry of silicon, but not of carbon, is expected to have the possibility of being influenced by the availability of empty 3d orbitals. Through the study of the reactions of various silylated organometallic compounds with common organic reagents, we have attempted to gain an insight into the chemistry of organosilicon compounds.

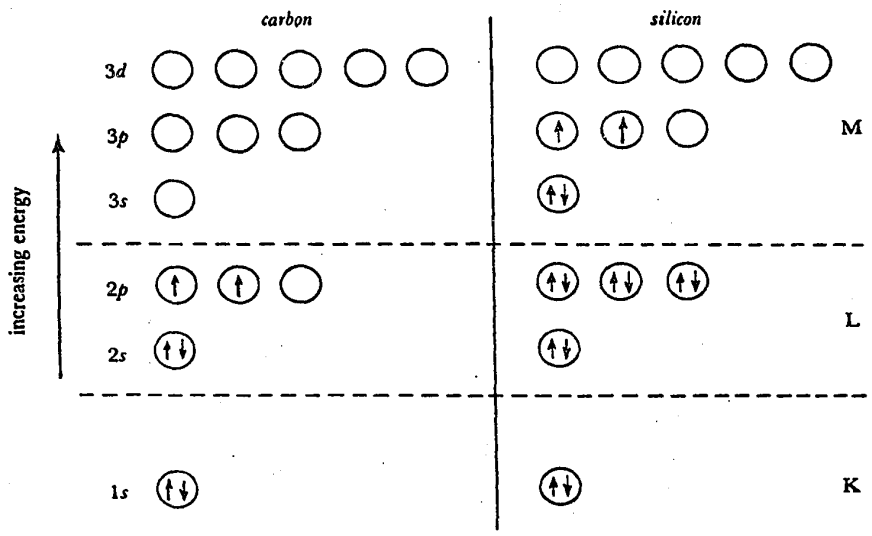
Some Aspects of Organosilicon Chemistry

Electronic Structure and Bonding

The ground state electronic configurations of carbon and silicon are shown in Fig. 1. The energy separation between the 2p and 3d orbitals of second row elements is so prohibitive that d orbitals in carbon are in effect of negligible use in bonding. For third row elements, the energy for promotion of an electron from the 3p to the 3d orbital is much smaller, and consequently, d orbitals take on far greater importance for silicon. In bonding, the valence shell orbitals of carbon undergo sp^3 hybridization giving carbon a normal valency of four and tetrahedral symmetry to carbon compounds (Fig. 2a). Silicon is usually also tetracovalent in organosilicon

Fig. 1

Electronic Configurations of Carbon and Silicon



Ref. 1

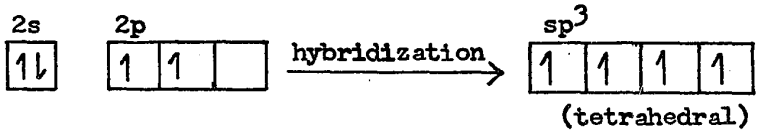
compounds and by analogy with carbon, we may reasonably suppose the bonds involved to be of the sp^3 type and the substituent groups to be tetrahedrally disposed in space (Fig. 2b).

Compounds containing carbon coordinated by more than four other groups are rare. The carbonyl complex $Fe_5(CO)_{15}C$ contains a single carbon atom in a square pyramid of iron atoms[2]; the interstitial carbides of NaCl structure, such as TiC, contain carbon atoms that are at least formally six-coordinated[3]. But these systems are exceptional. In marked contrast, higher coordination is common with silicon. It forms the hexafluorosilicate anion SiF_6^{-2} and compounds such as $Na_2Si(CH_3)F_5$ which probably contain analogous anions.[4] This indicates that silicon can expand its valence

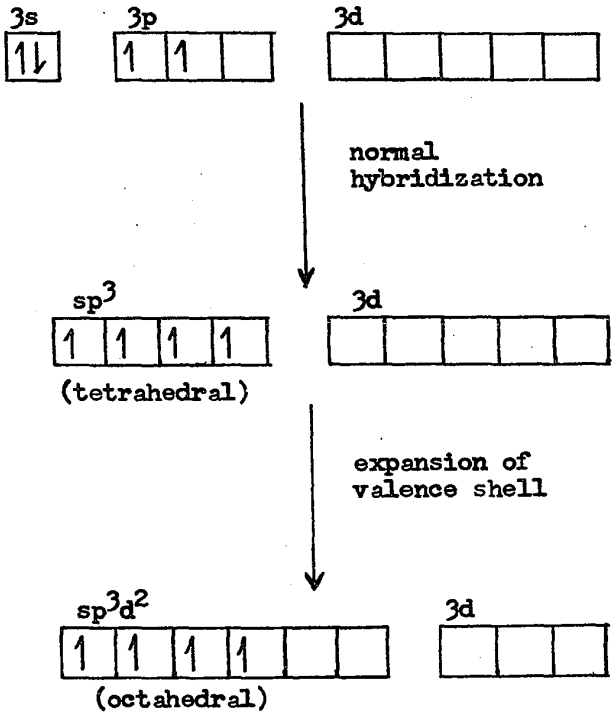
shell to accomodate 12 electrons by utilizing its 3d orbitals and undergoing sp^3d^2 hybridization. The resulting compounds have octahedral symmetry (Fig. 2b).

Fig. 2

a) Carbon Valence Shell



b) Silicon Valence Shell



(p ⟶ d)π Bonding

Compounds containing silicon double bonds of the type $>Si = Si<$, $>Si = C<$, $>Si = O$, or $>Si = N-$, are not known. In its inability to form the $p\pi - p\pi$ type of double bond, silicon resembles other third row elements such as sulphur and phosphorus. Nonetheless, silicon, like sulphur, does have a tendency to form a different type of double bond, involving d orbitals with elements like oxygen, nitrogen, and the halogens that have lone pair p electrons. This type of bonding is associated with $d\pi - p\pi$ overlap and is sometimes called "backbonding". It can be symbolized by the following resonance structures:

$$-\overset{\diagdown}{\underset{\diagup}{}}Si - \ddot{X} \longleftrightarrow -\overset{\diagdown}{\underset{\diagup}{}}\overset{-}{Si} = \overset{+}{X}$$

Examples of X include oxygen, nitrogen, halogens, as well as unsaturated groups like vinyl or phenyl.

The evidence in support of (p ⟶ d)π bonding is from several sources. First the lengths of Si — F, Si — Cl, Si — O, and Si — N bonds are all shorter than expected on the basis of ordinary single bonds (Table 1) indicating the possibility of at least partial double bond character.

Second the dipole moments of the halosilanes are all smaller than the dipole moments of the corresponding haloalkanes (Table 2) even though we would expect the opposite to be true if electronegativity effects were the only important factors, since the electronegativity of silicon is smaller than that of carbon (Table 3). Evidently the normal $\overset{\delta+}{Si} - \overset{\delta-}{X}$ bond polarity is offset by the electron

TABLE 1

LENGTHS OF SOME MA BONDS AS CALCULATED USING PAULING ELECTRONEGATIVITIES COMPARED WITH OBSERVED VALUES

A	M	r_{cal}, Å	r_{obs}, Å
C	C	1.54	1.53 (C_2H_6)
	Si	1.88	1.87 (CH_3SiH_3)
N	C	1.47	1.47 (Me_3N)
	Si	1.80	1.74 ($(SiH_3)_3N$)
O	C	1.42	1.42 (Me_2O)
	Si	1.76	1.63 ($(SiH_3)_2O$)
F	C	1.36	1.32 (CF_4)
	Si	1.70	1.54 (SiF_4)
Cl	C	1.72	1.77 (CCl_4)
	Si	2.05	2.01 ($SiCl_4$)
I	C	2.10	2.15 (CI_4)
	Si	2.44	2.43 (SiI_4)

Ref. 5

donation to silicon arising from (p → d)π bonding to a sufficient degree to reduce the Si — X bond moment below that of the C — X bond moment.

$$\text{ie. } H_3\overset{\delta+}{Si} - \overset{\delta-}{X} \longleftrightarrow H_3\overset{-}{Si} = \overset{+}{X}$$

Third replacement of carbon bound to nitrogen or oxygen by silicon reduces markedly the donor properties of the molecule in

TABLE 2

DIPOLE MOMENTS OF SOME SIMPLE COMPOUNDS OF CARBON AND SILICON (DEBYES)

Compound	X	Phase/solvent	M = C	M = Si
MHX_3	F	vapor	1.65	1.26
	Cl	vapor	1.03	0.85
	Br	heptane		0.79
		benzene	1.00	
MH_3X	F	vapor	1.81	1.27
	Cl	vapor	1.87	1.30
	Br	vapor	1.80	1.32

Ref. 6

TABLE 3

ELECTRONEGATIVITIES

Element	Electronegativity
Silicon	1.8
Carbon	2.5
Hydrogen	2.1
Oxygen	3.5
Phosphorous	2.3
Nitrogen	3.0
Sulphur	2.5
Chlorine	3.0

Ref. 7

question; stepwise replacement leads to a stepwise reduction of donor properties, for as donors the order of strength goes $C_3N > C_2NSi > CNSi_2 > NSi_3$[8,9] and $C_2O > COSi > OSi_2$[9,10]. This can best be explained by (p → d)π bonding.

Further, although less direct evidence relating to (p → d)π bonding has been obtained by studying the behaviour of R_3MOH and $(R_3M)_2NH$ (M = C or Si) as acids. In terms of electronegativity, increasing electron release to oxygen or nitrogen would be expected as M changes from carbon to silicon and this would be expected (in terms of current concepts in organic chemistry) to weaken the acidity of the -OH or -NH groups; thus R_3COH should be more acidic than say R_3SiOH. If, however, (p → d)π bonding were to change the σ-hybridization at nitrogen or oxygen from sp^3 to sp^2, the acidity of the hydrogen atom bound to nitrogen or oxygen would be expected to increase. This, in fact, was observed[11].

More evidence in support of (p → d)π bonding has been obtained from the study of ultraviolet, visible, electron spin resonance, nuclear magnetic resonance, nuclear quadrupole resonance, vibrational, and Mössbauer spectroscopy.[12]

The above evidence is not decisive, and it may be that some new theory will be able to account for all the observations, instead of most of them. But, at present the idea of (p → d)π bonding represents the simplest hypothesis that accounts for the greatest proportion of the observations; it should, therefore, be accepted on those terms, until a more satisfactory theory is advanced.

Bond Strengths

Silicon, like carbon, forms reasonably stable bonds to other silicon atoms, to carbon, hydrogen, the halogens, oxygen, and nitrogen. Some idea of the strengths of these bonds relative to analogous bonds involving carbon may be obtained from the average bond energies (Table 4). Significantly, the Si-Si bond is weaker than

TABLE 4

AVERAGE BOND ENERGIES

Bond	Energy (Kcal/mole)	Bond	Energy (Kcal/mole)
Si-Si	53	C-C	83
Si-C	76	C-Si	76
Si-H	76	C-H	99
Si-O	108	C-O	85
Si-N	77[a]	C-N	73
Si-F	135	C-F	116
Si-Cl	91	C-Cl	81
Si-Br	74	C-Br	68
Si-I	56	C-I	51

Ref. 13; a = Ref. 14.

the C-C bond by some 30 Kcal/mole, whereas the Si-O bond is stronger than the C-O bond by some 22 Kcal/mole. These bond energies account for several differences in the chemistry of the two elements. Thus, while carbon forms a great many compounds having linear and branched chains of C-C bonds, silicon is less versatile; the silanes of formula Si_nH_{2n+2} analogous to the alkanes of formula C_nH_{2n+2} are relatively unstable and react avidly with oxygen. On the other hand, the silicone polymers have chain networks of Si-O-Si bonds and have

a high thermal stability as corresponds to the considerable strength of the Si-O bond.

Preparation and Reactions of Silyl-Substituted Grignards and Alkali-Metal Compounds

Preparation

Whitmore and Sommer[15] and Hauser and Hance[16] showed that α-halosilanes react with magnesium to form the corresponding Grignard reagents in good yield. Thus:

$$(CH_3)_3Si - \underset{\underset{R}{|}}{CHX} + Mg \longrightarrow (CH_3)_3Si - \underset{\underset{R}{|}}{CHMgX}$$

R = H, CH_3, Ph
X = Cl, Br

However, diphenyl-α-chloromethyltrimethylsilane (I, X = Cl) and diphenyl-α-bromomethyltrimethylsilane (I, X = Br) failed to form the Grignard reagent under similar conditions[16].

$$(CH_3)_3SiC(Ph)_2$$
$$\underset{\underset{X}{|}}{}$$
$$\text{I}$$

It has been shown by Peterson[17,18] that silanes are metalated by the highly reactive n-butyllithium-tetramethylethylenediamine complex[19] (n-C_4H_9Li-TMEDA) to give the silyl-substituted alkyllithium compound. A few examples from Peterson's work follow:

$(CH_3)_4Si$ + n-C_4H_9Li-TMEDA $\longrightarrow$ $(CH_3)_3SiCH_2Li$

n-C_4H_9-$Si(CH_3)_3$ + n-C_4H_9Li-TMEDA $\longrightarrow$ n-C_4H_9-$Si(CH_3)_2CH_2Li$

$(CH_3)_3SiCH_2Ph$ + n-C_4H_9Li-TMEDA $\longrightarrow$ $(CH_3)_3SiCHPhLi$

The more reactive α-substituted phosphorus and sulphur silanes reacted with n-butyllithium alone without the addition of TMEDA. Thus: $(CH_3)_3SiCH_2R + n\text{-}C_4H_9Li \longrightarrow (CH_3)_3SiCHRLi$

R = Ph_2P, CH_3S

Chan et al[20] metalated benzyltrimethylsilane using n-butyllithium in hexamethylphosphoramide (HMPA) instead of TMEDA.

$$(CH_3)_3SiCH_2Ph \xrightarrow[HMPA]{n\text{-}BuLi} (CH_3)_3SiCHPh\ Li$$

Cason and Brooks[21] showed that an alkyllithium can add across the double bond of vinylsilane to give a metalated silane.

$$Ph_3SiCH=CH_2 + RLi \longrightarrow Ph_3SiCH(Li)\text{-}CH_2R$$

Brook et al[22] have shown that metal-halogen exchange occurs readily between an α-halosilane and n-butyllithium in ether.

$$Ph_3SiCH_2Br + n\text{-}BuLi \xrightarrow{Et_2O} Ph_3SiCH_2Li + n\text{-}BuBr$$

Reactions

Trimethylsilylacetone and related compounds have been prepared by the low temperature reaction of trialkylsilylmethyl Grignard reagents with acetic anhydride at -70° C, although the instability of the β-ketometalloids has led to some difficulty in isolation at times.[16,23]

$$R_3Si\text{-}CHMgCl(R') + R''COOCOR'' \xrightarrow[2)\ NH_4Cl/H_2O]{1)\ -70^\circ C} R_3Si\text{-}CHCOR''(R')$$

R = Me, Et; R' = H, Ph; R'' = Me, Ph.

Silyl-substituted Grignards react with acetonitrile in the following way:[16]

$$Me_3SiCHMgCl \xrightarrow{PhCN} Me_3SiCHC{=}NMgCl \xrightarrow[NH_4Cl]{H_2O} RCH_2COPh$$

Cleavage of the silyl group occurred on working up the reaction.

Silyl-substituted Grignards can be alkylated with alkyl halides. For example, with allyl bromide the following reaction takes place:[16]

$$Me_3SiCHMgCl + BrCH_2CH{=}CH_2 \longrightarrow Me_3SiCHCH_2CH{=}CH_2$$

R = H, Ph

Attempts to oxidize these silyl olefins with alkaline potassium permanganate to form carboxylic acids without cleaving the silicon-carbon bonds were unsuccessful.[16]

Hauser and Hance[16] treated trimethylsilylmethylmagnesium chloride with ketones to yield β-silyl carbinols:

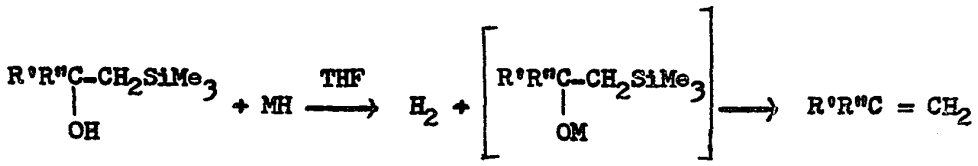
$$Me_3SiCH_2MgCl + R'COR'' \longrightarrow R'R''C(OMgCl)-CH_2SiMe_3 \xrightarrow{H^+} R'R''C(OH)-CH_2SiMe_3$$

a) $R' = CH_3$, $R'' = CH_3$

b) $R' = Ph$, $R'' = H$

These carbinols did not undergo elimination of Me_3SiOH under acidic conditions.

Peterson[18] and Chan et al[20] treated some β-silyl carbinols with sodium or potassium hydride in tetrahydrofuran to give the sodium or potassium salts which readily eliminated Me_3SiOM to yield an olefin:

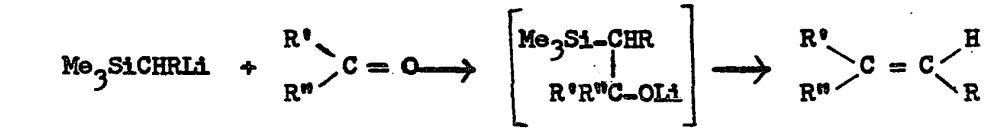


M = Na or K;

	R'	R''
a)	CH_3	CH_3
b)	H	Ph
c)	H	$n\text{-}C_7H_{15}$
d)	Ph	Ph
e)	CH_3	$CH_2CH_2CH = C(CH_3)_2$
f)	$-(CH_2)_5-$	

Together, the last two series of reactions constitute a method for the synthesis of olefins from carbonyl compounds complementing the Wittig reaction[24] and Corey's olefin synthesis with sulfinamide.[25]

The usefulness of the methylene extension reaction using silylalkyl-Grignard reagents is limited by the availability of the precursory chloroalkylsilanes. However, this type of olefination reaction has been achieved by the use of silylalkyllithium reagents which are easily prepared from the readily available parent silanes as was shown above. The following silylalkyllithium reagents were reacted with various carbonyl compounds to give the olefin in one step:[18,20]



R = Ph, Ph_2P, CH_3S;

R'	R''
Ph	Ph
Ph	H
CH_3	CH_3
$-(CH_2)_5-$	

Substituted ethylidenes have been prepared[20] by the following sequence of reactions:

$$Ph_3SiCH = CH_2 \xrightarrow{RLi} Ph_3SiCH\text{-}CH_2R \xrightarrow{R'R''CO} \begin{matrix} R' \\ R'' \end{matrix}\!\!>\!C = C\!<\!\begin{matrix} H \\ CH_2R \end{matrix}$$

a) R = n-Bu, R' = Ph, R'' = H

b) R = n-Bu, R' = CH_3, R'' = $-CH_2CH_2CH = C(CH_3)_2$

In this thesis the reactions of silyl-substituted Grignard and lithium-metal reagents with acid chlorides and anhydrides will be described.

Preparation and Reactions of Alkali-Metal and Magnesium Derivatives of Organosilicon Compounds Having Metal-Metal Bonds

The study of silylorganometallic compounds containing metal-metal bonds has been an area of active research during recent years. These highly reactive intermediates are well established and usefully employed in syntheses. The most important compounds of this type are those containing bonds of silicon with magnesium and the alkali metals; lithium, sodium, and potassium. They have been described in reviews.[26-29]

Preparation of Alkali-Metal Silyl Compounds

Early unsuccessful attempts:- Attempts to prepare silylmetallic compounds employing methods which are useful for organometallic compounds were unsuccessful.

The reactions of metals with organic halides is perhaps the most fundamental one for the preparation of organometallic compounds.[30] However, when trialkyl- and triaryl-silyl halides were reacted with

alkali metals, only disilanes were isolated, although the process may involve the formation of a silylmetallic intermediate which reacts with another mole of silyl halide.[31]

$$R\text{-}Cl + 2Na \longrightarrow R\text{-}Na + NaCl$$

$$R_3Si\text{-}Cl + 2Na \longrightarrow [R_3Si\text{-}Na] + NaCl$$

$$[R_3Si\text{-}Na] \xrightarrow{R_3SiCl} R_3Si\text{-}SiR_3 + NaCl$$

Numerous examples of metalations of the type, $RH + R'Li \longrightarrow RLi + R'H$ are known in carbon chemistry.[32] Corresponding reactions of Si-H with organolithium compounds resulted in the displacement of a hydride ion and the formation of a new Si-C bond.[33]

$$R_3Si\text{-}H + R'Li \longrightarrow R_3SiR' + LiH$$

Whereas triphenylmethane reacts with potassium amide to give triphenylmethylpotassium,[34] related reactions of triphenylsilane give silylamines.[35]

$$Ph_3C\text{-}H + KNH_2 \longrightarrow Ph_3C\text{-}K + NH_3$$

$$Ph_3Si\text{-}H + LiNR_2 \longrightarrow Ph_3Si\text{-}NR_2 + LiH$$

Halogen-metal interconversion is another choice method for preparing many organometallic compounds.[30] Silyl halides generally yield coupling products when allowed to react with organoalkali-metal compounds.[36]

$$RX + R'Li \longrightarrow RLi + R'X$$

$$R_3SiX + R'Li \longrightarrow R_3SiR' + LiX$$

In special cases where halogen-metal interconversion occurs in silicon chemistry, as in the reaction between silyl halides and the stilbene-dilithium adduct,[37] the silyllithium intermediate couples immediately with the silyl halide to give a disilane as the final product:

$$R_3SiCl + (CHPhLi)_2 \longrightarrow PhCH=CHPh + LiCl + [R_3Si\text{-}Li] \xrightarrow{R_3SiCl} R_3Si\text{-}SiR_3 + LiCl$$

From disilanes:- The most convenient preparative method of silyl-alkali-metal compounds, and one of general applicability, is the cleavage of disilanes by alkali-metal in an ether solvent such as tetrahydrofuran (THF) or ethylene glycol dimethyl ether (GDME).[38-43]

$$R_3Si\text{-}SiR_3 + 2M \xrightarrow{\text{ether solvent}} 2R_3Si\text{-}M$$

R = alkyl, aryl, or H; M = alkali metal

At least two of the R groups must be aryl for the cleavage to occur. $(Alkyl)_3SiM$ compounds useful for synthetic purposes have not yet been successfully prepared this way.[44] However, examples of this class, Et_3SiLi and Me_3SiLi, can be made[45,46] by treatment of the mercurials[47] $EtHgSiEt_3$, $(Et_3Si)_2Hg$, or $(Me_3Si)_2Hg$ with lithium in tetrahydrofuran.

Of all the ether solvents tried tetrahydrofuran, in a procedure developed by Gilman and Lichtenwalter,[39] has proved to be the best. The yields in this synthesis are very good; the triphenylsilyllithium compound they made is soluble, and the solutions are

quite stable at room temperature. On the other hand, the triphenylsilylalkali-metal compounds are insoluble in diethyl ether[40] and unstable, although soluble, in ethylene glycol dimethyl ether[41]. Tetrahydropyran or dioxane can also be used to prepare triphenylsilyllithium this way.[48,49] Although the silyllithium compound is more stable in these solvents than in tetrahydrofuran, its rate of formation is slower in these solvents. Thus, tetrahydrofuran is the most advantageous solvent to use.

From silyl halides:- While disilanes are usually prepared by the reaction of chlorosilanes with alkali metals, and silylmetallic compounds are prepared by the metal-cleavage of disilanes as seen above, methods have been investigated to combine these two steps by a proper choice of metal and solvent. It was found that silyl halides do react with alkali metals to give silylalkali-metal compounds. The reaction is thought to proceed in two steps:

$$R_3Si\text{-}Cl + 2M \longrightarrow \left[R_3Si\text{-}M\right] + MCl \xrightarrow{R_3SiCl} R_3Si\text{-}SiR_3 + 2MCl$$

$$R_3Si\text{-}SiR_3 \xrightarrow{2M} 2\ R_3Si\text{-}M$$

M = alkali metal

R = alkyl, aryl, or H

Chlorotriphenylsilane was converted into triphenylsilylpotassium by the use of sodium-potassium alloy in ether,[40,50] whereas in xylene the reaction stops at the disilane stage.[50] By using lithium in tetrahydrofuran it is possible to prepare several silyllithium compounds directly from the corresponding chlorosilanes. Ph_3SiLi,[51]

$MePh_2SiLi$[49], $Me_2PhSiLi$[52], and Ph_2HSiLi[43] were prepared by this method. Trialkylchlorosilanes are converted into disilanes by lithium in THF; no further cleavage occurs.[26]

The use of chlorosilanes may be advantageous in many cases (for example, triphenylchlorosilane costs about one tenth as much as hexaphenyldisilane); however, the yields of the silylmetallic reagents often appear to be slightly lower than from the corresponding disilanes. Furthermore, chlorosilanes, though commercially available, require special precautions owing to their ease of hydrolysis.

In comparison with silyllithium and silylpotassium derivatives, silylsodium has been used very little. Sodium dispersion in ether, tetralin, xylene, or dioxane[40] did not affect cleavage of disilanes. When ethylene glycol dimethyl ether or tetrahydrofuran was used as solvent, the cleavage by sodium went smoothly.[41]

Eisch[53] has shown that solutions of biphenyl-lithium complexes in tetrahydrofuran are very remarkably effective in promoting certain cleavage reactions which proceed only slowly, or not at all, with the bulk metal.

From alkoxysilanes:- Alkoxysilanes such as ethoxytriphenylsilane[50] and methoxytriphenylsilane[54] have been used for the preparation of triphenylsilylpotassium by cleavage with sodium-potassium alloy in diethyl ether. This reaction may also involve the intermediate formation of hexaphenyldisilane. Thus:

$$Ph_3Si\text{-}OR + Na/K \xrightarrow{Et_2O} Ph_3Si\text{-}K \xrightarrow{Ph_3Si\text{-}OR} Ph_3Si\text{-}SiPh_3 \xrightarrow{Na/K} Ph_3Si\text{-}K$$

Wittenberg et al[55] prepared Ph_2SiHLi from $Ph_2SiH(OCHPh_2)$ in the following way:

$$Ph_2SiH(OCHPh_2) + Ph_3SiLi \longrightarrow Ph_3Si\text{-}SiPh_2H + Ph_2CHOLi$$

$$Ph_3Si\text{-}SiPh_2H \xrightarrow{Ph_3SiLi} Ph_3Si\text{-}SiPh_3 + Ph_2SiHLi$$

From silanes:- The preparation of R_3SiM compounds from hydrides[56] is usually used only in selected cases, ie.

$$(Ph_3Ge)_3Si\text{-}H + Li \longrightarrow (Ph_3Ge)_3Si\text{-}Li$$

Usually when a hydride is used, disproportionation occurs. For example, when triphenylsilane was reacted with lithium in tetrahydrofuran, tetraphenylsilane and a number of other products were obtained.[54]

$$Ph_3SiH + 2Li \longrightarrow Ph_2SiHLi + PhLi \xrightarrow{+2Li} PhSiHLi_2 + 2PhLi$$

$$PhLi + Ph_3SiH \longrightarrow Ph_4Si + LiH$$

$$Ph_4Si + 2Li \longrightarrow Ph_3SiLi + PhLi$$

$$n\ Ph_2SiHLi \longrightarrow n\ LiH + (Ph_2Si)_n$$

$$n\ PhSiHLi_2 \longrightarrow n\ LiH + (PhSiLi)_n$$

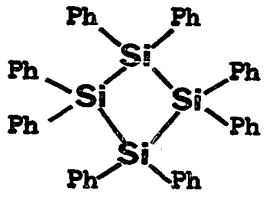
Similar disproportionation products were obtained when Ph_2SiH_2 and $PhSiH_3$ were used.[54] This interfering disproportionation makes the preparation of silyl-alkali-metal compounds from silanes impractical.

Gilman and co-workers[55,57] prepared triphenylsilylsodium, 1,4-disodiooctaphenyltetrasilane (II, M = Na), and 1,5-disodiodecaphenylpentasilane (III, M = Na) by treatment of cyclo- or polysilanes with an excess of sodium in the presence of catalytic quantities of naphthalene or biphenyl. ie.

$MSiPh_2(SiPh_2)_2SiPh_2M$ II

$MSiPh_2(SiPh_2)_3SiPh_2M$ III

$$Ph_3Si(SiPh_2)_2SiPh_3 + 2Na \rightarrow \begin{cases} 2Ph_3Si\text{-}SiPh_2Na \\ Ph_3Si\text{-}SiPh_2SiPh_2Na + Ph_3SiNa \end{cases}$$

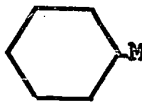
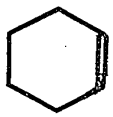


$$+ 2Na \xrightarrow[\text{or Ph-Ph (cat.) in THF}]{\text{naphthalene (cat.)}} Na(SiPh_2)_4Na$$

In a similar manner 1,4-dilithiooctaphenyltetrasilane (II, M = Li) and 1,5-dilithiodecaphenylpentasilane (III, M = Li) were obtained by the cleavage of the corresponding cyclosilane with lithium in tetrahydrofuran in the presence of biphenyl or naphthalene. The yield of these dilithio compounds was increased 20-30% over that with lithium alone.

Preparation of Magnesium-Metal Silyl Compounds

Silyl halides react with Grignards[58] or magnesium metal[52] in tetrahydrofuran to yield only disilanes. However, a silyl Grignard intermediate is believed to be formed. Thus, with Grignards:

$$Ph_3SiCl + 2\,\text{  }MgBr \xrightarrow{THF} [Ph_3SiMgBr] + \text{  } + \text{  }$$

$$+ MgClBr$$

$$\text{or } Ph_3SiCl + 2PhMgBr \xrightarrow{THF} [Ph_3SiMgBr] + Ph\text{-}Ph + MgClBr$$

$$\text{and } Ph_3SiMgBr + Ph_3SiCl \rightarrow Ph_3Si\text{-}SiPh_3 + MgClBr$$

The formation of $Ph_3SiMgBr$ as an intermediate was confirmed by employing a mixture of triphenyl- and trimethylchlorosilane which yielded 1,1,1-trimethyl-2,2,2-triphenyldisilane, the unsymmetrical coupling product:

$$Ph_3SiMgBr + Me_3SiCl \longrightarrow Ph_3Si\text{-}SiMe_3$$

When magnesium metal was reacted with halosilanes, the following was observed:

$$Ph_3SiCl + Mg \xrightarrow{THF} \left[Ph_3SiMgCl\right] \xrightarrow{Ph_3SiCl} Ph_3Si\text{-}SiPh_3 + MgCl_2$$

Thus, magnesium is not effective in rupturing the silicon-silicon bond to give the corresponding silylmagnesium derivative in the same way as alkali metals are.

Calas et al[59] reacted aromatic ketones with magnesium and chlorotrimethylsilane in hexamethylphosphoramide to yield bis-trimethylsilylmethanes in the following way: (see, however, p. 25)

$$\rangle C{=}O + 2Mg + 4ClSiMe_3 \xrightarrow{HMPA} \rangle C\langle^{SiMe_3}_{SiMe_3} + 2MgCl_2 + Me_3SiOSiMe_3$$

A silyl Grignard intermediate ($Me_3SiMgCl$) is probably formed in the course of the reaction.

Reactions of Silylalkali-Metal Compounds

With carbonyl compounds:

Silylalkali-metal derivatives react with CO_2 to yield the silyl acid.[26,29,46,48,60]

$$R_3SiM + CO_2 \longrightarrow R_3SiCOOH$$

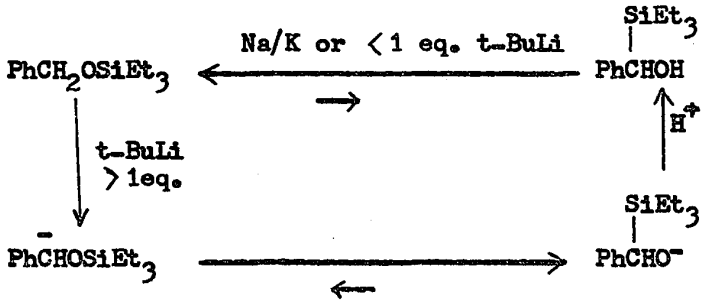
The reaction with aliphatic aldehydes and ketones gives silyl carbinols.[26,29,60-62]

$$R_3SiM + R'R''C{=}O \longrightarrow R_3Si\text{-}CR'R''OH$$

With arometic aldehydes and ketones, the initially formed adduct rearranges under the reaction conditions to give the following:[27,38]

$$Ph_3SiLi + PhCOR \longrightarrow \left[Ph_3Si\text{-}CPhROLi\right] \longrightarrow Li\text{-}CPhROSiPh_3 \xrightarrow{H_2O} HCPhROSiPh_3$$

However, West et al[63] have shown that when alkoxysilanes are treated with more than one equivalent of ter-butyllithium, a rearrangement takes place to give the α-silyl carbinol after hydrolysis with dilute acid. They also found that the α-silyl carbinol, when treated with sodium-potassium alloy or less than one equivalent of ter-butyllithium, rearranged to the alkoxysilane. These rearrangements are summarized in the following cyclic reaction scheme:



Thus, when neutral species are equilibrated, as with sodium-potassium alloy, the alkoxysilane is more prevalent, because of the greater stability of the Si-O bond. However, when anions are equilibrated, the equilibrium lies in the opposite direction because the greater stability of the oxyanion versus the carbanion outweighs the energy difference between the Si-O and C-O bonds.

With derivatives of carboxylic acids:

Triphenylsilyllithium reacts with acetyl chloride[64,65] as follows:

$$Ph_3SiLi + MeCOCl \longrightarrow Ph_3SiCOMe \xrightarrow{Ph_3SiLi} (Ph_3Si)_2CMe(OH)$$

$$\downarrow \text{rearranges}$$

$$(Ph_3Si)CHMe(OSiPh_3)$$

Acetic anhydride and ethyl acetate on treatment with triphenylsilyllithium gave results[61,64] similar to those observed in the acetyl chloride reaction.

With C-C multiple bonds:

Reactions involving addition of silyllithium reagents to olefinic, acetylenic, or aromatic compounds are synthetically useful. Triphenylsilyllithium adds readily to polyphenyl olefins:[66]

$$Ph_3SiLi + Ph_2C = CH_2 \longrightarrow Ph_3SiCH_2\text{-}CPh_2Li$$

$$" + PhCH = CHPh \longrightarrow Ph_3SiCHPh\text{-}CHPhLi$$

$$" + Ph_2C = CHPh \longrightarrow Ph_3SiCHPh\text{-}CPh_2Li$$

$$" + Ph_2C = CPh_2 \longrightarrow \text{no addition product}$$

while triethylsilyllithium adds to propylene, 1-hexene, and styrene:[46]

$$Et_3SiLi + RCH = CH_2 \longrightarrow Et_3SiCH_2\text{-}CHRLi$$

R = Me, n-Bu, Ph.

With organic halides:

The reactions of silylalkali-metal reagents with alkyl or aryl halides provides an alternate route to the preparation of unsymmetrically substituted tetraorganosilanes.[26-29]

$$R_3SiM + R'X \longrightarrow R_3SiR' + MX$$

R' can be alkyl, aryl, or even unsaturated, as for example[67]

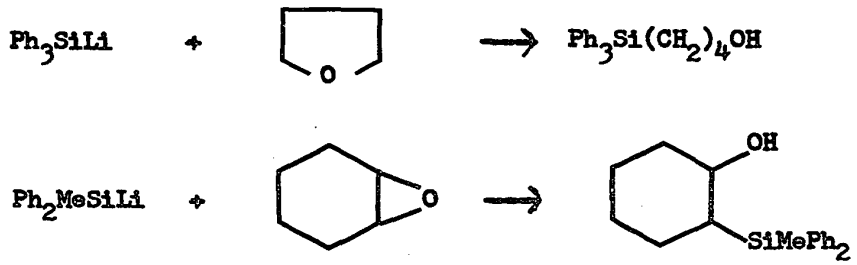
$$Ph_3SiLi + CH_2 = CHCH_2Cl \longrightarrow CH_2 = CHCH_2SiPh_3 + LiCl$$

An eight membered ring has been made this way:[68]

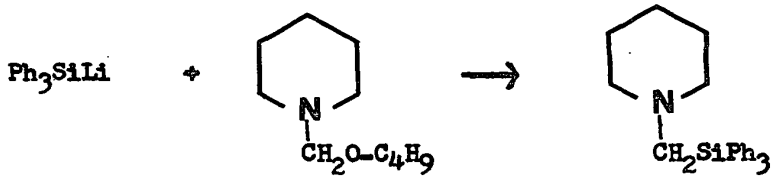
$$Li(Ph_2Si)_5Li + Cl(CH_2)_3Cl \longrightarrow \underline{CH_2(Ph_2Si)_5CH_2CH_2}$$

With oxygen compounds:

An excellent method developed by Gilman and co-workers for the preparation of silyl-substituted derivatives is the ring opening of heterocycles, including epoxides, by silyl-alkali-metal compounds.[26,29] For example:



Silylalkali-metal reagents with oxygen compounds give the following:[26,29]



$$Ph_3SiLi + PhOMe \longrightarrow Ph_3SiMe$$

and with silyl ethers disilanes are formed[69]

$$Ph_3SiLi + Ph_3SiOEt \longrightarrow Ph_3SiSiPh_3$$

The reaction of triphenylsilyllithium with tosyl esters gives the following products:[29]

$$Ph_3SiLi + n\text{-}BuOTs \longrightarrow Ph_3Si(n\text{-}Bu)$$

$$Ph_3SiLi + Ph_3Si(CH_2)_3OTs \longrightarrow Ph_3Si(CH_2)_3SiPh_3$$

Silylalkali-metal compounds react with phosphate esters in the following way:[29]

$$R_3SiM + (R'O)_3PO \longrightarrow R_3SiR'$$

R = alkyl, aryl, or alkylsilyl*; R' = alkyl

$$*(Me_3Si)_3SiLi + (MeO)_3PO \longrightarrow (Me_3Si)_3SiMe$$

<u>With nitrogen compounds:</u>

Triphenylsilyllithium reacts with primary and secondary amines to give silyl amines.[26,29]

$$Ph_3SiLi + R_2NH \longrightarrow Ph_3SiH + R_2NLi$$

$$\downarrow$$

$$LiH + Ph_3Si\text{-}NR_2$$

Triphenylsilylpotassium or -lithium adds to the azo linkage in the following manner:[26]

$$Ph_3SiK + PhN{=}NPh \xrightarrow{H_2O} Ph_3SiPhN\text{-}NHPh$$

and to benzophenone anil as follows:[26,29]

$$Ph_3SiK + Ph_2C{=}NPh \xrightarrow{H_2O} Ph_2CH\text{-}NPhSiPh_3$$

The hydrolysis products, $Ph_2CH\text{-}NHPh$ and Ph_3SiOH are also formed.

With organosulphur compounds:

Only a few reactions between silylmetallic compounds and organosulphur compounds have been investigated. The reaction of diphenyl sulphide with triphenylsilyllithium, followed by carboxylation, gave benzoic acid and thiophenol as well as hexaphenyldisilane.[70] The following sequence of reactions is believed to take place.

$$Ph_2S + Ph_3SiLi \longrightarrow PhLi + Ph_3Si\text{-}SPh$$

$$Ph_3Si\text{-}SPh + Ph_3SiLi \longrightarrow PhSLi + Ph_3Si\text{-}SiPh_3$$

$$Ph_3Si\text{-}SiPh_3 \xrightarrow{\text{carboxylation}} PhCOOH + PhSH$$

With miscellaneous compounds:

Reactions of silylmetallic derivatives with miscellaneous compounds are shown below:[29]

$$Ph_3SiLi + Ph_3CH \longrightarrow Ph_3SiH + Ph_3CLi$$

$$Ph_3SiLi + Ph_3SiH \longrightarrow Ph_4Si + LiH + Ph_3Si\text{-}SiPh_3$$

$$Ph_3SiLi + (p\text{-}MeC_6H_4)_2Hg \longrightarrow p\text{-}MeC_6H_4SiPh_3 + p\text{-}MeC_6H_4HgLi$$

In this thesis the reactions of magnesium metal and chlorotrimethylsilane in hexamethylphosphoramide with carbonyl compounds will be discussed. The products found were different from those reported by Calas et al[59] (cf. p. 20).

RESULTS AND DISCUSSION

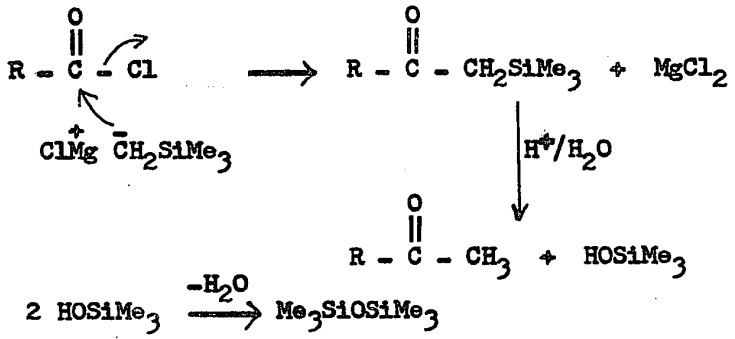
The Reactions of Silyl-Substituted Organometallic Compounds with Acid Chlorides and Anhydrides

The Reaction of Trimethylsilylmethylmagnesium Chloride with Acid Chlorides

The facile conversion of β-silyl ketones to ketones is well known[71] ($R\text{-}CO\text{-}\overset{|}{\underset{|}{C}}\text{-}SiR'_3 \xrightarrow[H_2O]{H^+} R\text{-}CO\text{-}\overset{|}{\underset{|}{C}}H + HOSiR'_3$). Its synthetic potential appears not to have been explored. Trimethylsilylmethylmagnesium chloride (IV) was prepared by the method of Whitmore and Sommer[15] by reacting magnesium with chloromethyltrimethylsilane as was seen above. This silyl Grignard was stable for quite a long

$$Me_3SiCH_2Cl + Mg \xrightarrow[R.\ T.]{\text{ether}} \underset{\text{IV}}{Me_3SiCH_2MgCl}$$

time (ie. its titre remained constant) when kept dry and under nitrogen in the refrigerator. It was titrated prior to each use by the method of Gilman.[72] The reaction of this reagent with a number of aromatic and aliphatic acid chlorides afforded, after hydrolysis with dilute hydrochloric acid, the corresponding methyl ketones (Table 5). The reaction probably takes the following course:



For simplicity, the Grignard reagent will be represented throughout this thesis as a simple ionic species, although its structure and mode of reaction is much more complex. It could, of course, react as a free radical instead of as an anion as is pictured above.

TABLE 5

REACTIONS OF TRIMETHYLSILYLMETHYLMAGNESIUM CHLORIDE WITH ACID CHLORIDES

$Me_3SiCH_2MgCl + RCOCl \longrightarrow RCOCH_3$

R-	Derivative by which $RCOCH_3$ was characterized	mp(°C)	Lit. mp.(°C)	% Yield
Ph-	2,4-DNPH	244 (mixed mp)	238-40	70
$CH_3(CH_2)_4$-	2,4-DNPH	88-90	89	46
m-Cl-C_6H_4-	oxime	85-86	88	50
$CH_3(CH_2)_8$-	2,4-DNPH	62-63	63	52
C_5H_9-CH_2CH_2-	2,4-DNPH	87.5-88	new cpd.	85
p-Me-C_6H_4-	2,4-DNPH	258-9	258	73
p-Cl-C_6H_4-	2,4-DNPH	230-1	231	55
C_6H_{11}-	2,4-DNPH	132-8	140	71

Usually ketones can be prepared from acid halides and organo-Grignard reagents only in unsatisfactory yields[73], exceptions being, as a rule, to be ascribed to steric hindrance.[74] Primarily for this reason, the organozinc[75] and organocadmium[76-78] compounds are used

in the synthesis of ketones, the use of Grignard reagents giving rise to the formation of tertiary alcohols.[73] Therefore, when one tries to make methyl ketones from the corresponding acid halides by reacting them with methylmagnesium chloride, the initial ketone formed competes with the acid halide in reacting with the highly reactive Grignard reagent. Thus, the methyl ketone cannot be isolated in good yield; instead mainly the dimethyl carbinol is isolated after work-up.[73]

ie. $CH_3MgCl + RCOCl \longrightarrow RCOCH_3 + MgCl_2$

$RCOCH_3 \xrightarrow{CH_3MgCl} RC(CH_3)_2OH$

When the silyl Grignard reagent is used, perhaps the presence of the bulky trimethylsilyl group makes the initial ketone formed too sterically hindered to further attack by another bulky trimethylsilylmethyl anion. Unfortunately, the reaction of the carbon analogue of trimethylsilylmethylmagnesium chloride, ie. neopentylmagnesium chloride, with acid chlorides was never studied. However, Blomberg and Mosher[79] reacted neopentylmagnesium chloride with benzophenone. They found firstly, through ESR studies, that the reaction proceeds via a free radical mechanism. Secondly, they found the products to be a mixture of 1,1-diphenyl-3,3,-dimethylbutanol, benzopinacol, and neopentane. Thus,

$$Me_3CCH_2MgCl + PhCOPh \xrightarrow{THF} Me_3CCH_2\text{-}CPh_2OH + Ph_2COHCOHPh_2 + Me_4C$$

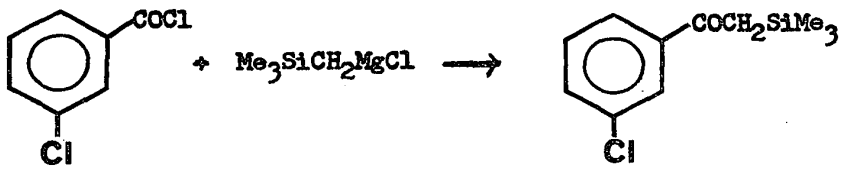
The steric bulk of the neopentyl group (R^t) so retards the normal addition reaction ($Ph_2CO + R^tMgCl \longrightarrow Ph_2R^tCOMgCl$) that the radicals formed in the process ($Ph_2CO + R^tMgCl \longrightarrow Ph_2\dot{C}OMgCl + {}^\circ R^t$) are able to escape from the solvent cage. The neopentyl radical can then react with the solvent to give neopentane and the ketyl radical can dimerize to give the magnesium chloride salt of benzopinacol. Thus, the steric factor may play an important role in retarding the addition of a second mole of trimethylsilylmethylmagnesium chloride to the initial ketone formed.

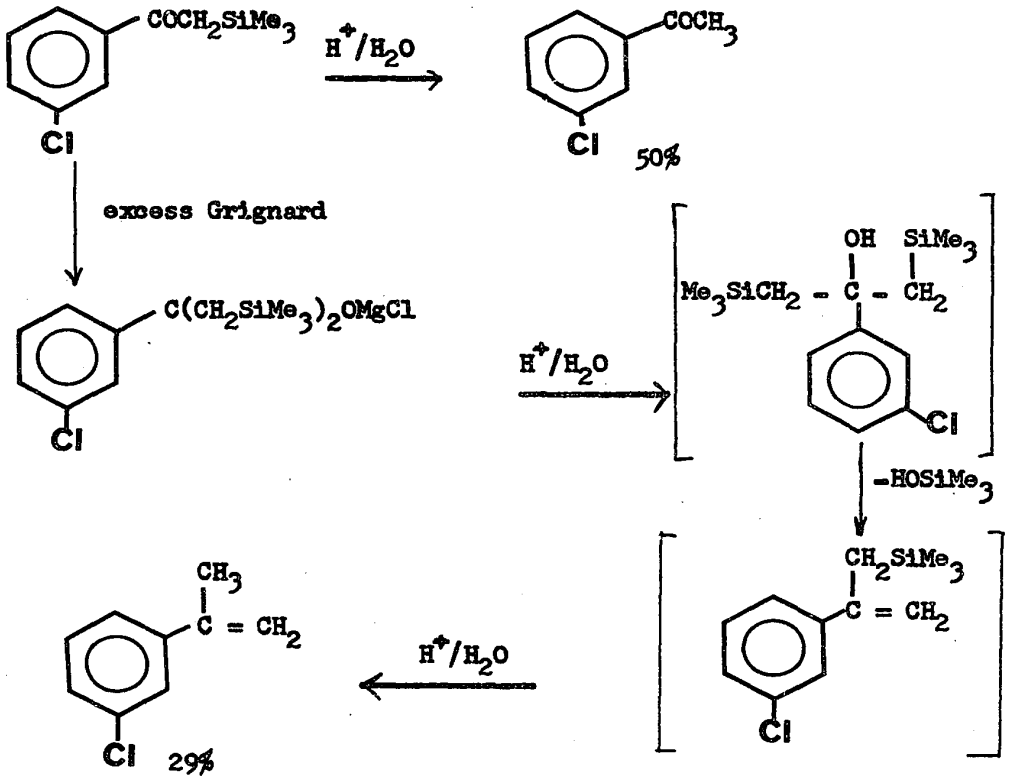
In addition, the silyl Grignard itself may be less reactive than the corresponding carbon compound, since the electron density on the carbon atom adjacent to silicon can spread into the empty d orbitals of silicon in (p $\rightarrow$ d)π bonding. The following resonance structures can be written:

$$\bar{C}H_2 - SiMe_3 \longleftrightarrow CH_2 = \bar{S}iMe_3$$

and so it does not react with the ketone when the more reactive acid chloride is present.

In the reaction of trimethylsilylmethylmagnesium chloride with meta-chlorobenzoyl chloride, the Grignard reagent was, unfortunately, used in 23% excess, and so the excess Grignard reacted with the initial ketone formed to give 1-methyl-1-(3')-chlorophenylethylene in 29% yield. Thus,





Reactions of the type shown in the last step of this sequence are known[80]

$$Me_3SiCH_2\underset{\displaystyle R}{\overset{|}{C}} = CH_2 \xrightarrow{HCl} CH_3\underset{\displaystyle R}{\overset{|}{C}} = CH_2 + Me_3SiCl$$

R = H, Me

Had the Grignard been used in a 1:1 molar ratio, the yield of the methyl ketone would have been higher. These results seem to indicate that the steric factor is not as important in the silyl Grignard case as with neopentylmagnesium chloride since the silyl Grignard reacted with a highly hindered ketone. Since it does not react with the initial ketone formed when used in a 1:1 molar ratio, and

reacts preferentially with the acid chloride, the reactivity factor seems to be quite important.

This method of preparing methyl ketones gives fairly satisfactory yields. It can also be adapted to forming other ketones by using different silyl-substituted Grignards or silyl-substituted lithium compounds. The latter was used to test the general applicability of this reaction.

The Reaction of Trimethylsilylphenylmethyllithium with Benzoyl Chloride

Trimethylsilylphenylmethyllithium (V) was prepared just prior to use by the method of Petersen[17,18] by reacting benzyltrimethylsilane with the n-butyllithium-tetramethylethylenediamine complex as was seen above. ie.

$$Me_3SiCH_2Ph + n\text{-}BuLi\text{-}TMEDA \longrightarrow \underset{V}{Me_3Si\overset{-}{C}H\overset{+}{P}hLi}$$

The red carbanion solution of V was then reacted with benzoyl chloride to yield, after hydrolysis with dilute acid, desoxybenzoin (VI) in 45% yield. Thus,

$$\underset{V}{Me_3Si\overset{-}{C}H\overset{+}{P}hLi} + PhCOCl \longrightarrow PhCOCHPhSiMe_3 \xrightarrow{H^+/H_2O} \underset{VI}{PhCOCH_2Ph}$$

Therefore, the reaction of silyl-substituted organometallic compounds with acid chlorides to yield ketones seems to be of general applicability. This method will now be compared with other methods of preparing ketones from simple carboxylic acid derivatives.

Other General Methods for Preparing Ketones from Simple Carboxylic Acid Derivatives

With organozinc compounds:

$$RCOCl + R'ZnCl \text{ or } R'_2Zn \longrightarrow RCOR' + ZnCl_2$$

Although Blaise[75] originally claimed excellent yields in this type of preparation, a succession of investigators[81] has failed to obtain better than moderate yields. The organozinc reagent is difficult to prepare and reacts with the carbonyl group to some extent. On the other hand, silyl-substituted organometallic compounds are prepared easily and do not react with the carbonyl group when used in a 1:1 molar ratio.

With Grignard reagents:

The common idea of the impossibility of ketone synthesis from $R'MgX$ and $RCOCl$[73] is true only for small R groups; steric hindrance in either R or R' is sufficient to yield the desired ketones[74], although considerable quantities of the tertiary alcohol were always produced. Thus,

$$RCOCl + R'MgX \longrightarrow RCOR' + RR'_2COH$$

The reverse addition of acid chloride to the Grignard reagent increased the yield of the ketone produced.[82] However, the yields were never very high and the tertiary alcohols were always formed to some extent. Silyl-substituted organometallic compounds give good yields and do not react further with the carbonyl group when used in a 1:1 molar ratio.

With organocadmium compounds:

Ketones have been prepared by the reaction of organocadmium compounds with acid chlorides[76,78] and with acid anhydrides[77], the latter giving inferior yields.

$$\begin{matrix} RCOCl \\ or \\ (RCO)_2O \end{matrix} + R'_2Cd \longrightarrow RCOR'$$

This reaction is successful for aromatic and primary alkyl cadmium derivatives only. Secondary and tertiary cadmium derivatives are stable only at low temperatures ($< 0^{\circ}C$) and so are difficult to prepare and use and also give very poor yields of ketones. The silyl-substituted organometallic compounds are stable at room temperature and secondary derivatives can be used (eg. compound V). Like the organocadmium compounds, silyl-substituted organometallic compounds do not react further with the carbonyl group when used in a 1:1 molar ratio. Yields, in the preparation of ketones from cadmium reagents can be greatly reduced by an incorrect experimental procedure[78], and so the reaction is quite cumbersome to carry out.

With organolithium compounds:

Gilman and Van Ess[83] prepared ketones by reacting organolithium compounds with lithium salts of carboxylic acids.

$$RCOOH \xrightarrow{R'Li} RCOOLi \xrightarrow{R'Li} RCOR' \qquad \begin{matrix} R = Pr, Ph \\ R' = Ph \end{matrix}$$

The ketone can be prepared directly from the acid in one step by using two moles of R'Li, but they[83] found that some tertiary alcohol

was also formed.

$$RCOOH + 2\ R'Li \longrightarrow RCOR' + RR'_2COH$$

They[83] also found that the reaction with acid chlorides gave only tertiary alcohols; no ketone at all was formed.

$$RCOCl + R'Li \longrightarrow RR'_2COH$$

The reaction of carboxylic acids with organolithium compounds is presently the best general method available for making ketones.[84] The main disadvantages are that very low temperatures must be used with the more reactive alkyllithium reagents and that tertiary alcohols are often formed as side products. More extensive study on the reaction with silyl-substituted organometallic compounds is necessary before it can compete with organolithium compounds as a general method for ketone synthesis from carboxylic acids.

With diazomethane:

Acid chlorides react with diazomethane to give diazoketones which have been transformed into methyl ketones by a variety of ways.[85]

$$RCOCl + CH_2N_2 \longrightarrow RCOCHN_2$$

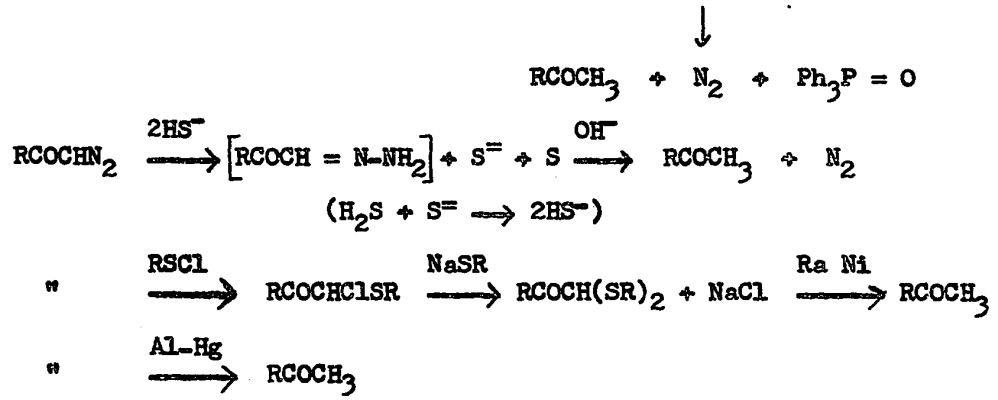
$$RCOCHN_2 \xrightarrow{HI} RCOCH_2I + N_2 \xrightarrow{HI} RCOCH_3 + N_2 + I_2$$

$$" \xrightarrow{\text{cat. } H_2} RCOCH_3 + 2NH_3$$

$$" \xrightarrow{HBr} RCOCH_2Br \xrightarrow{SnCl_2} RCOCH_3$$

$$" \xrightarrow{Ph_3P} RCOCH = N\text{-}N = PPh_3 \xrightarrow{H_2O} \left[RCOCH = N\text{-}NH_2\right] + Ph_3P = O$$

$$\left[RCOCH = N\text{-}NH_2\right] \xrightarrow{OH^-}$$

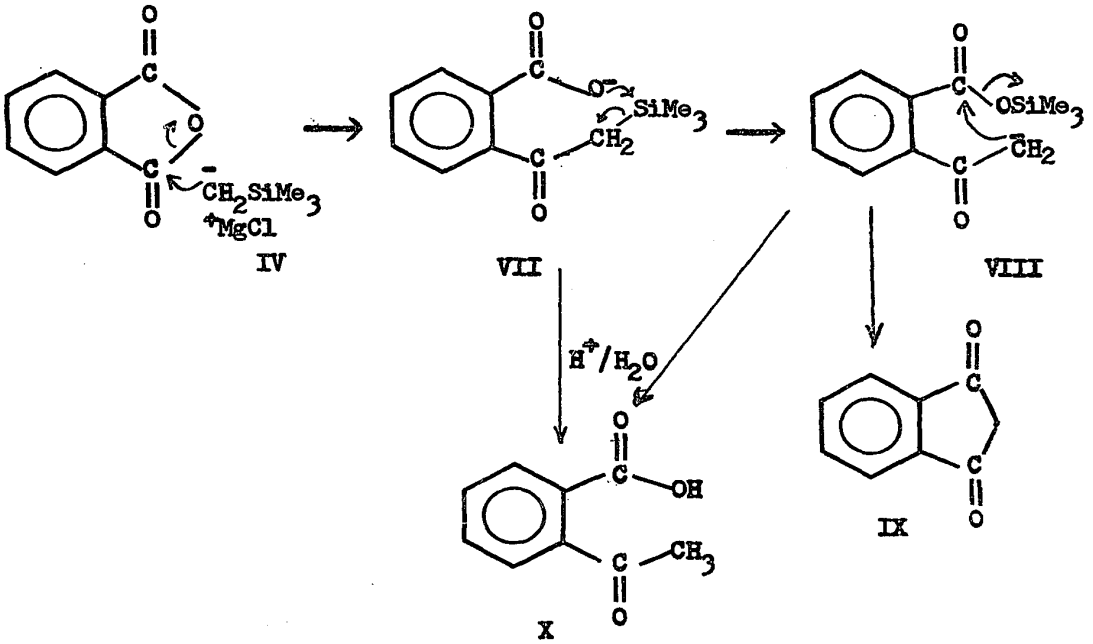


Only methyl ketones can be made made from diazoketones and so this methed is very limited in scope.

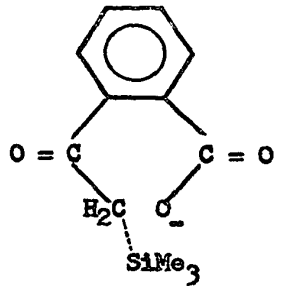
The Reaction of Trimethylsilylmethylmagnesium Chloride with Anhydrides

With phthalic anhydride:

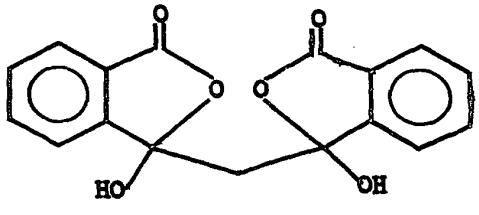
The reaction of trimethylsilylmethylmagnesium chloride (IV) with phthalic anhydride was expected to take the following course:



It was thought that the first step would be attack by the carbanion of the Grignard reagent on the anhydride to yield intermediate VII, followed by migration of the trimethylsilyl group to form the stronger O-Si bond of intermediate VIII. The migration was expected to take place because intermediate VII is a planer and rigid molecule. The oxygen atom to which the silyl group would migrate and the carbon atom to which it is attached are in the same plane and in close proximity. Thus,

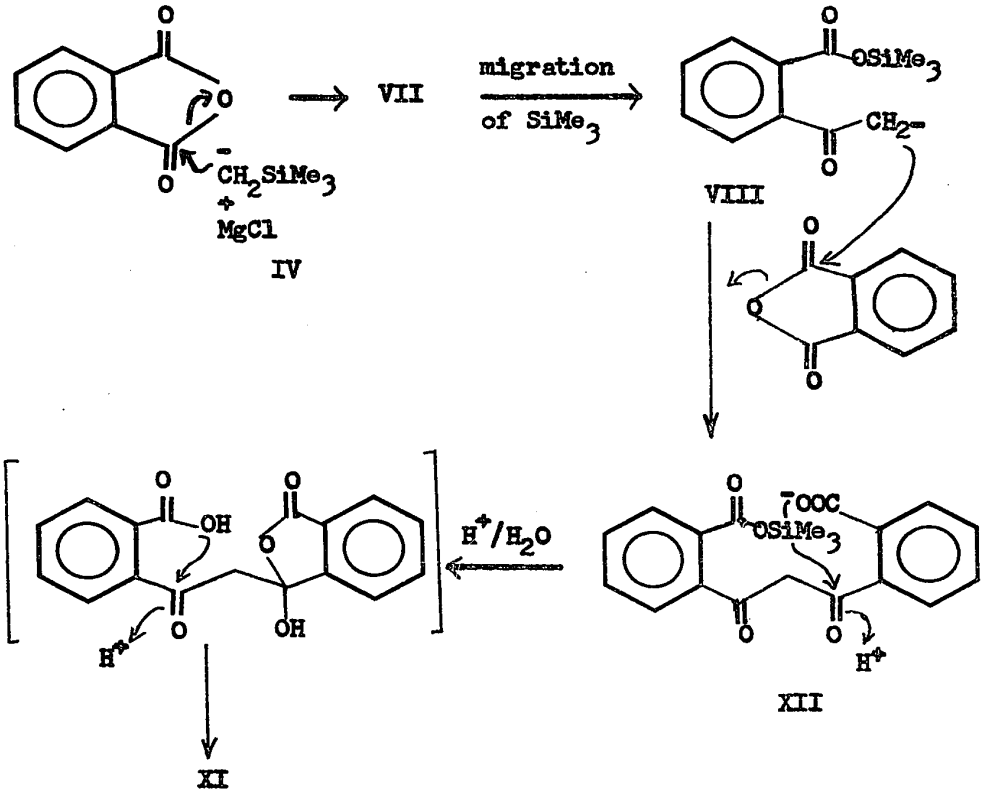


It was then thought that intermediate VIII would collapse to give 1,2-benzocyclopenta-3,5-dione (IX), and/or hydrolysis of either VIII or VII would give 2-carboxyacetophenone (X) as products. However, the product isolated in 63% yield had structure XI. It was a white crystalline meterial which melted at 168-9°C. (Proof of structure, p. 68). The following reaction mechanism was postulated to explain



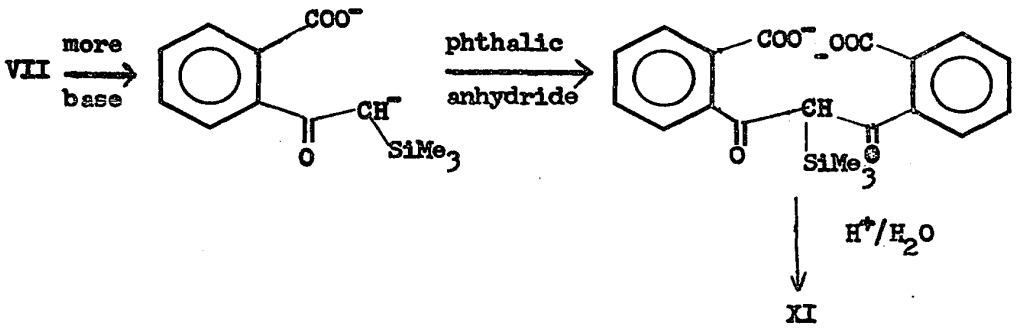
XI

the formation of the γ-lactone (XI):



As expected, the trimethylsilyl group migrates to the oxygen of intermediate VII to give intermediate VIII. Then, instead of collapsing to give the 1,3-diketone (IX), as expected, intermediate VIII reacts with another molecule of phthalic anhydride to give intermediate XII which is hydrolyzed by acid to the γ-lactone (XI).

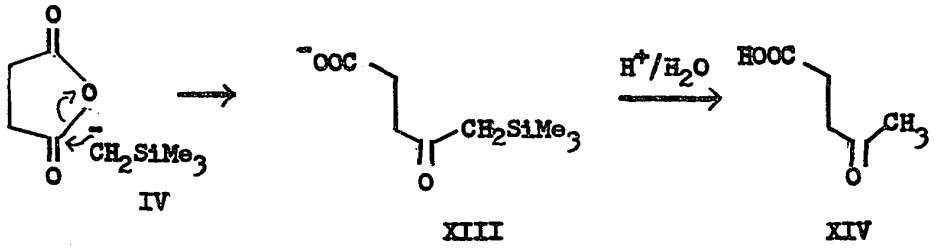
An alternate mechanism, not involving migration, can be written as follows:



This mechanism, however, requires that two anions be in close proximity, and so is not very likely.

With succinic anhydride:

The reaction of trimethylsilylmethylmagnesium chloride (IV) with succinic anhydride was not expected to follow the same course because the molecule is not rigid. The following was expected to occur instead:

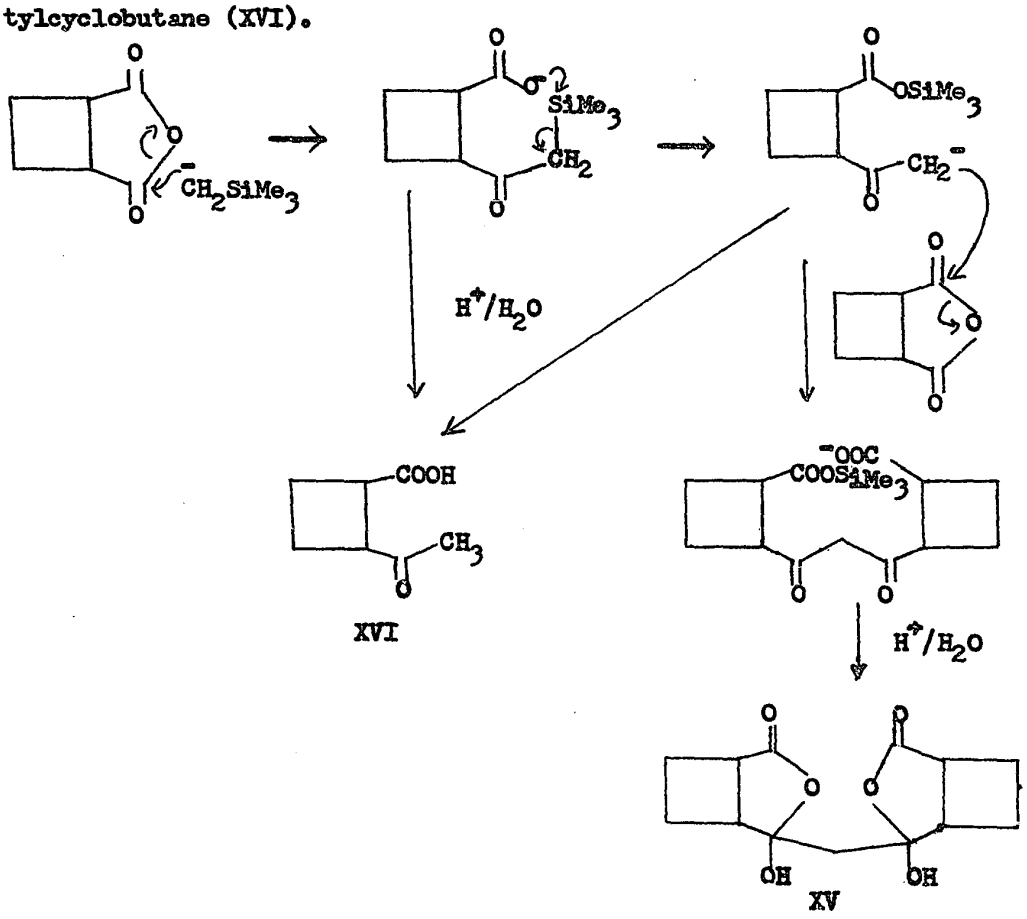


It was expected that attack by the silyl Grignard would give intermediate XIII. However, the silyl group was not expected to migrate to the oxygen atom in this case since intermediate XIII is capable of free rotation, and so the oxygen atom to which the silyl group might have rotated and the carbon atom to which it is attached are not close to each other. Hydrolysis of intermediate XIII should

give 1-carboxybutane-3-one (XIV) as the product. However, the only product that was isolated in this reaction was succinic acid which arises from the hydrolysis of the starting material, and so no reaction at all seems to have taken place.

With cis-1,2-cyclobutanedicarboxylic anhydride:

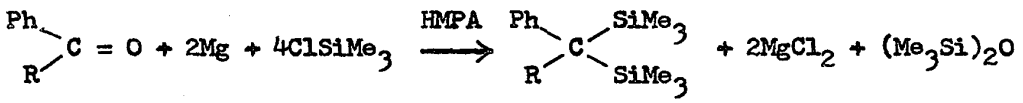
It was thought that the reaction of trimethylsilylmethyl-magnesium chloride (IV) with cis-1,2-cyclobutanedicarboxylic anhydride would give a product similar to that of the reaction with phthalic anhydride; the silyl group of the first intermediate formed would be in close proximity to the carboxylate oxygen and so would migrate to it. The final product was expected to be the γ-lactone (XV). Hydrolysis of either intermediate would give 1-carboxy-2-acetylcyclobutane (XVI).



However, there was no evidence of the γ-lactone in the residual oil when this reaction was carried out, and the products were a mixture that could not be positively identified. There seemed to be the carboxylic acid functional group present as well as the trimethylsilyl ether group.

The Reaction of Trimethylsilylmagnesium Chloride with Aldehydes and Ketones

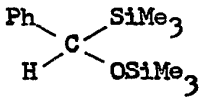
Calas et al[59] reported the following reaction as was seen earlier (p. 20).



R = Ph, CH_3, H

XVII

Trimethylsilylmagnesium chloride is presumed to be formed in situ and reacts immediately with the carbonyl compound to eventually form the bis(trimethylsilyl)methane (XVII). In the reaction with benzaldehyde they isolated the siloxy compound (XVIII) as an intermediate.



XVIII

We thought that it would be interesting to measure the pKa's of bis(trimethylsilyl)phenylmethane (XIX) and of benzyltrimethylsilane (XX), and to compare them with those of toluene, diphenylmethane, and triphenylmethane, in order to see how the replacement of successive hydrogens by trimethylsilyl groups affects the acidity of the molecule. However, when an attempt was

$Ph\text{-}CH(SiMe_3)_2$ $Ph\text{-}CH_2(SiMe_3)$ $PhCHOH\text{-}CHOHPh$

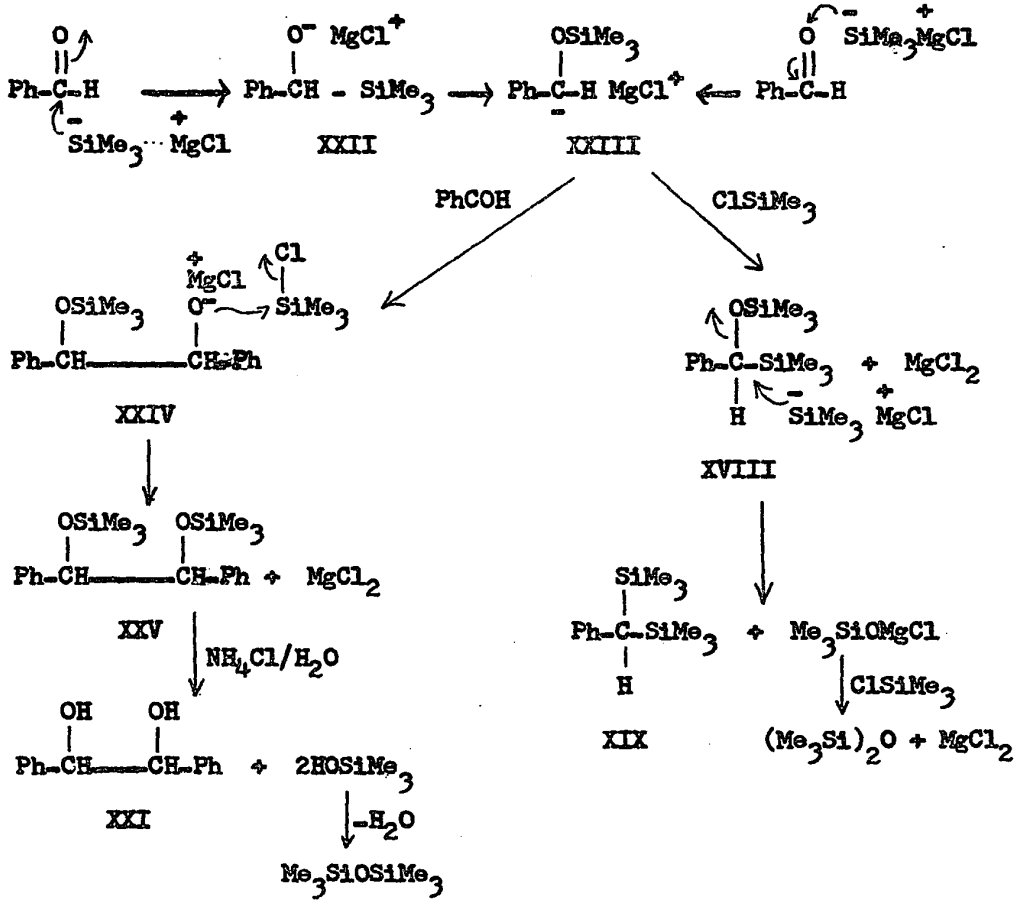
XIX XX XXI

made to synthesize compound XIX by following the procedure of Calas,[59] the main product was a mixture of the meso and dl forms of 1,2-diphenylethane-1,2-diol (XXI), formed in 85% yield. The possible mechanisms in the reaction of benzaldehyde with magnesium and chlorotrimethylsilane in hexamethylphosphoramide are outlined in Fig. 3. The Grignard is again denoted as a simple ionic species although it may react as a free radical as well. In any case, the silyl Grignard should either attack the carbonyl group in the normal manner to give intermediate XXII followed by rearrangement to carbanion XXIII[27,38,61] or else the silyl Grignard could attack the carbonyl group at the oxygen atom giving carbanion XXIII immediately. Carbanion XXIII can then react with either chlorotrimethylsilane or benzaldehyde, depending on which is more readily available, to give either intermediate XVIII or intermediate XXIV, respectively. Structure XVIII is the intermediate isolated by Calas[59] in this reaction. It can react with another mole of the silyl Grignard to yield bis(trimethylsilyl)-phenylmethane (XIX); whereas intermediate XXIV reacts with another mole of chlorotrimethylsilane to give the trimethylsilyl ether XXV, which upon hydrolysis with dilute acid yields the pinacol XXI. The hydrolysis of XXV is carried out using a very weak acid (NH_4Cl/H_2O) to prevent the rearrangement of XXI to the pinacolone. ie.

$$\underset{\text{XXI}}{PhCH(OH)\text{-}CH(OH)Ph} \xrightarrow{H^+} Ph_2HC\text{-}C(=O)H$$

Fig. 3

The Possible Mechanisms in the Reaction of Benzaldehyde with Magnesium and Chlorotrimethylsilane in Hexamethylphosphoramide



In the reaction conditions followed[59] the magnesium and chlorotrimethylsilane were mixed together in hexamethylphosphoramide and heated up to 110°. Then the benzaldehyde, dissolved in the same solvent, was added slowly and the mixture was stirred at 95° for

seventy-five hours. Thus, the chlorotrimethylsilane should have been in excess at all times. However, if the magnesium did not start reacting with the chlorotrimethylsilane to form the Grignard at the start of addition of the benzaldehyde, but only after it had all been added, then the entire quantity of benzaldehyde that was used was present in the reaction vessel throughout the course of the reaction and so the second reaction path was followed yielding the pinacol. It seems that the silyl Grignard is more reactive toward benzaldehyde than toward chlorotrimethylsilane, since although the latter was present in great excess at all times, the Grignard reacted preferentially with benzaldehyde. In any case, a new and efficient method of reducing ketones and aldehydes to pinacols was found.

Most of the known methods for the reduction of aromatic ketones and aldehydes to the corresponding pinacols leave much to be desired. The reduction with amalgamated aluminum[86] in benzene gives fairly poor yields (~30%) and the resulting metal pinacolate forms a thick voluminous gel, difficult to stir. Electrolytic methods[87] use acidic or basic media not suitable for sensitive ketones and aldehydes and the establishment of the optimum set of parameters for each new case is tedious. Benzophenone was reduced with magnesium or magnesium iodide[88] in ether-benzene to give benzopinacol in 99% yield. However, when we tried to reduce benzaldehyde with magnesium or magnesium and iodine in hexamethylphosphoramide, no reaction occurred (see p. 44). So this method[88] seems to work only for benzophenone. Photochemical[89] reduction of aromatic ketones and alde-

hydes to the corresponding pinacols gives excellent yields and is a very simple and clean reaction. However, for large-scale preparations, it would require a very long time. It is even more difficult to reduce aliphtic ketones and aldehydes to the corresponding pinacols.[90]

The general applicability of the reduction with magnesium and chlorotrimethylsilane in hexamethylphosphoramide was tested by repeating the reaction with some aromatic and aliphatic ketones. The reaction conditions were changed in that the chlorotrimethylsilane was added slowly to a mixture of the carbonyl compound and magnesium in hexamethylphosphoramide in order to make sure that the carbonyl compound was in excess.

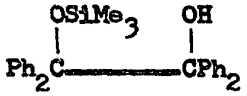
With benzaldehyde:

The reaction of chlorotrimethylsilane and magnesium in hexamethylphosphoramide with benzaldehyde was repeated using the modified reaction conditions to test the postulated mechanism. 1,2-diphenylethane-1,2-diol (XXI) (meso and dl forms) was again formed in 90% yield. No reaction occurred under the same reaction conditions when no chlorotrimethylsilane was added, and so its presence is necessary for the reaction to take place.

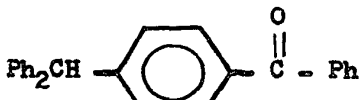
With benzophenone:

The reaction of chlorotrimethylsilane and magnesium in hexamethylphosphoramide with benzophenone was expected to yield benzopinacol. However, only 16% of 2-trimethylsiloxytetraphenylethanol (XXVI) was isolated. The main product was p-benzoyltriphenylmethane

(XXVII) formed in 68% yield. It was compared to an authentic sample

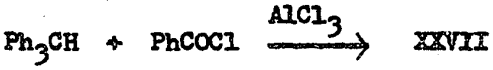


XXVI



XXVII

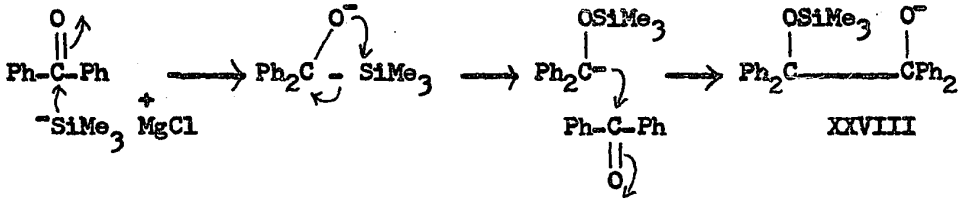
made by the Friedel-Craft reaction of triphenylmethane with benzoyl chloride. Thus,



The IR, NMR, and mass spectra of the two samples were identical.

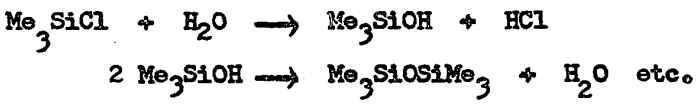
Several mechanisms were proposed for the reaction of benzophenone with chlorotrimethylsilane and magnesium in hexamethylphosphoramide.

Mechanism 1:

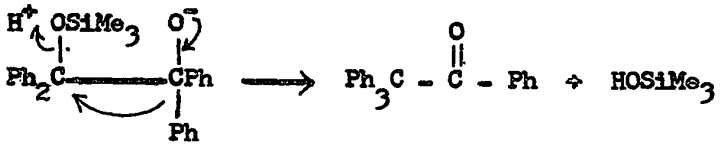


XXVIII

In the presence of even a minute quantity of water, some of the chlorotrimethylsilane is hydrolyzed to hydrochloric acid and trimethylsilanol. ie.

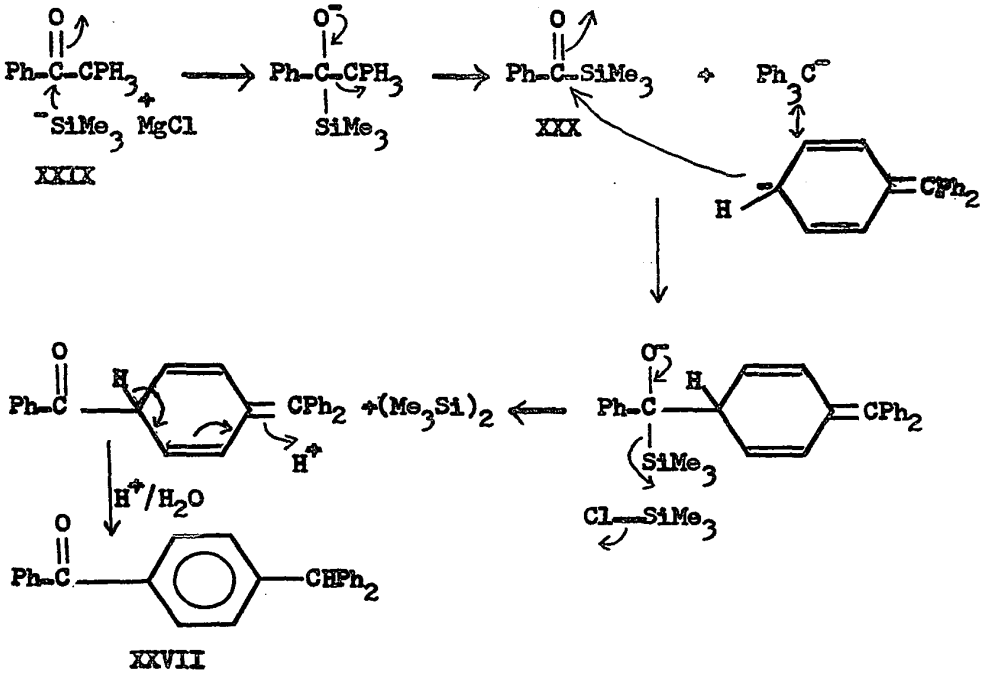


Therefore intermediate XXVIII can undergo the equivalent of a pinacol rearrangement. Thus,



XXVIII XXIX

Another molecule of the Grignard can then add to the benzopinacolone (XXIX) formed to give p-benzoyltriphenylmethane (XXVII) in the following manner:



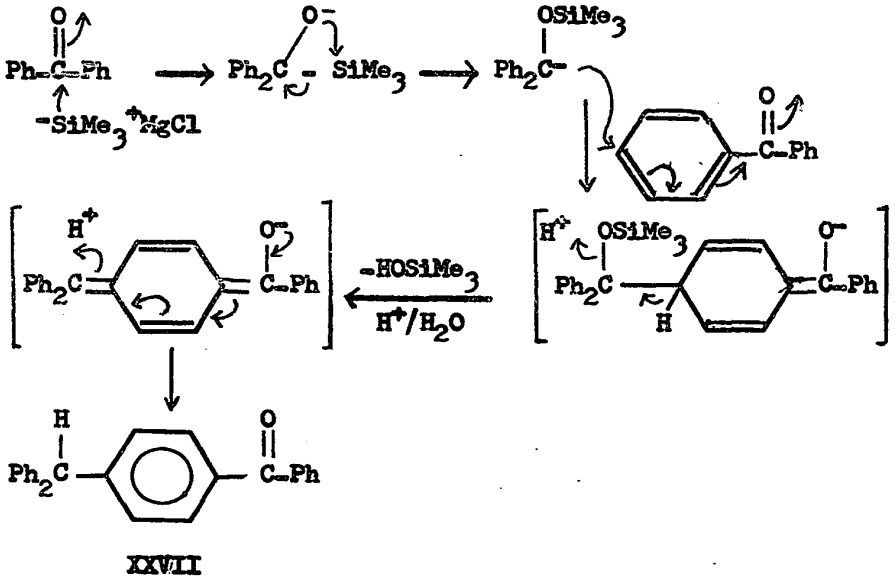
XXVII

A trityl anion is visualized which attacks the silyl ketone (XXX), formed as an intermediate, via its other resonance form because of steric hindrance at the carbonyl group due to the presence of the bulky trimethylsilyl group and the phenyl group.

This mechanism was tested by reacting benzopinacolone (XXIX), which was postulated as an intermediate in the reaction, under the

same reaction conditions with chlorotrimethylsilane and magnesium. However, no p-benzoyltriphenylmethane (XXVII) was formed and so this mechanism was rejected.

Mechanism 2:

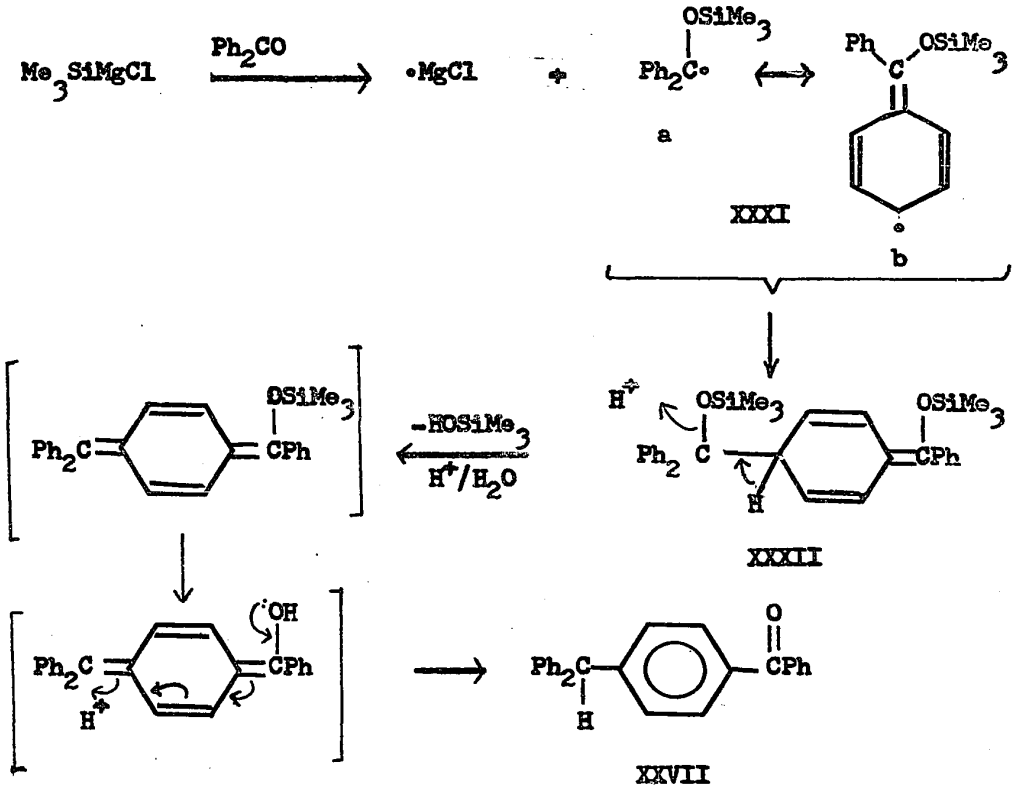


XXVII

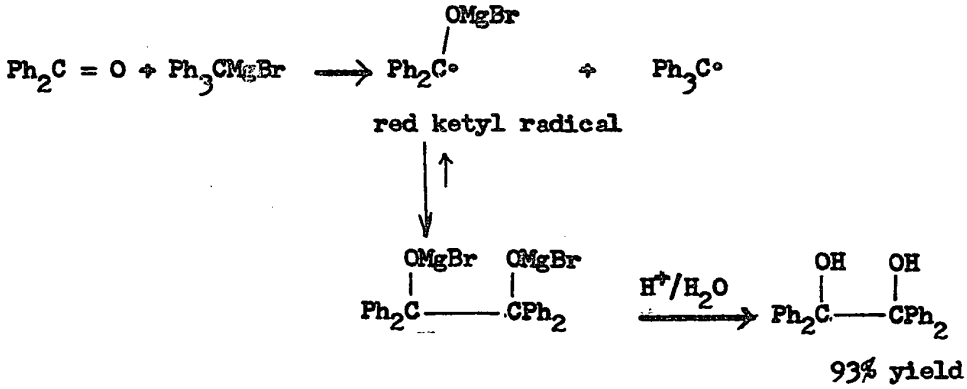
In this mechanism, the siloxy anion attacks another molecule of benzophenone at the para position of the phenyl ring rather than at the carbonyl carbon atom because of steric hindrance. The intermediate so formed can then be hydrolyzed by dilute acid to p-benzoyltriphenylmethane (XXVII).

Mechanism 3:

A free radical mechanism was postulated to explain the intense blue colour of the reaction mixture.



There are examples in the literature to make one believe that the free radical mechanism is the most likely one. When Bachmann [91] reacted benzophenone with tritylmagnesium bromide, he found that the main product was benzopinacol which can arise only by a free radical mechanism in the following manner:



Blomberg and Mosher[79] reacted benzophenone with neopentylmagnesium chloride and also found that the reaction proceeded via a free radical mechanism. Thus,

$$Ph_2C=O + Me_3CCH_2MgCl \xrightarrow{THF} Ph_2C^{\bullet}(OMgCl) + Me_3CCH_2^{\bullet}$$

$$Ph_2C(OMgCl)-CH_2CMe_3 \xrightarrow{H^+/H_2O} Ph_2C(OH)-CH_2CMe_3$$

$$\text{and } 2\ Ph_2C^{\bullet}(OMgCl) \longrightarrow Ph_2C(OMgCl)-CPh_2(OMgCl) \xrightarrow{H^+/H_2O} Ph_2C(OH)-CPh_2(OH)$$

$$Me_3CCH_2^{\bullet} \xrightarrow{THF} Me_4C$$

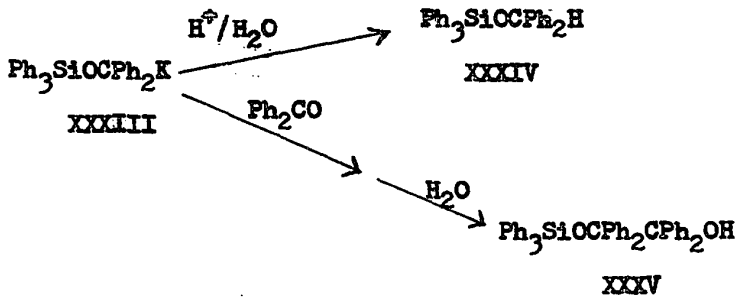
In these reactions with alkyl or aryl Grignards, the authors postulated the formation of the ketyl radical, $Ph_2\dot{C}OMgX$. In the reaction with silyl Grignard, we postulated the formation of the siloxy radical (XXXI) because of the great strength of the Si-O bond. Schwartz and Brook[92] isolated a similar siloxy intermediate from the reaction of triphenylsilylpotassium with benzophenone. They believed this intermediate to be triphenylsiloxydiphenylmethylpotassium (XXXIII). ie.

$$Ph_3SiK + Ph_2CO \longrightarrow Ph_3SiOCPh_2K$$

XXXIII

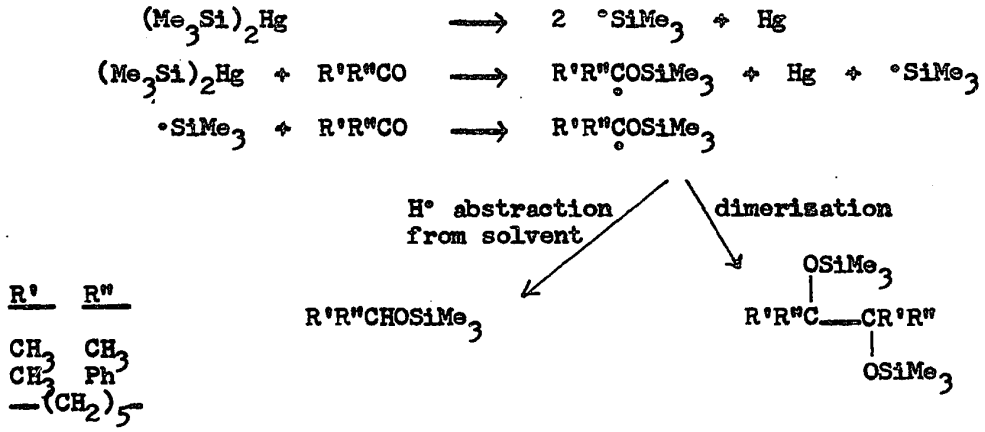
This material is believed to be the precursor of benzhydryloxytriphenylsilane (XXXIV), originally reported as the main product of the reaction (see p. 21), and also of 2-triphenylsiloxytetraphenyl-

ethanol (XXXV). ie.



Wittenberg, Wu, and Gilman[93] have described rather similar reactions for the reaction of triphenylsilyllithium with benzaldehyde, although the identity of some of their products, especially the analogue of XXXIII, was not uniquely established.

These reactions seem to indicate that an ionic mechanism is at work when one reacts triphenylsilyl-alkali-metal compounds with benzophenone or benzaldehyde. However, when trimethylsilylmagnesium chloride is used, a free radical mechanism might prevail, as was postulated above. Beaumont et al[94] postulated a free radical mechanism for the reaction of bis(trimethylsilyl)mercury with various ketones to give as products the corresponding oxysilane and O,O-bis(trimethylsilyl)pinacol. Thus,



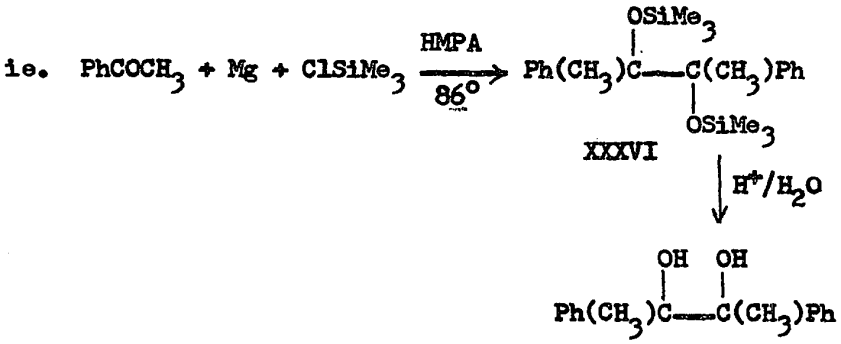
Unfortunately, they did not carry out the reaction with benzophenone. It would be interesting to see if the product would be p-benzoyltriphenylmethane of benzopinacol (after hydrolysis). Neumann and Neumann[95] described a similar reaction for aryl aldehydes. They, however, found that the ketones that Beaumont et al[94] had used did not react at all, or reacted only very sparingly, with bis(trimethylsilyl)mercury.

In the mechanism postulated for the formation of p-benzoyltriphenylmethane (p. 48), radical XXXI can exist in more than one resonance form (eg. a and b). Because of steric hindrance form a does not dimerize to yield the precursor of benzopinacol in the same way that the ketyl radicals and siloxy radicals of less hindered ketones do. Instead, forms a and b combine to give intermediate XXXII which is hydrolyzed to p-benzoyltriphenylmethane (XXVII). The siloxy radical (XXXI) cannot abstract a hydrogen atom from the solvent, which is hexamethylphosphoramide, to give the benzhydrylsiloxy compound analogous to those reported by Beaumont et al[94].

The reaction with benzaldehyde, in which the mixture also turned intense blue, probably also goes via a free radical route similar to mechanism 3, but one gets the pinacol because the replacement of a phenyl group by a hydrogen atom removes the steric hindrance.

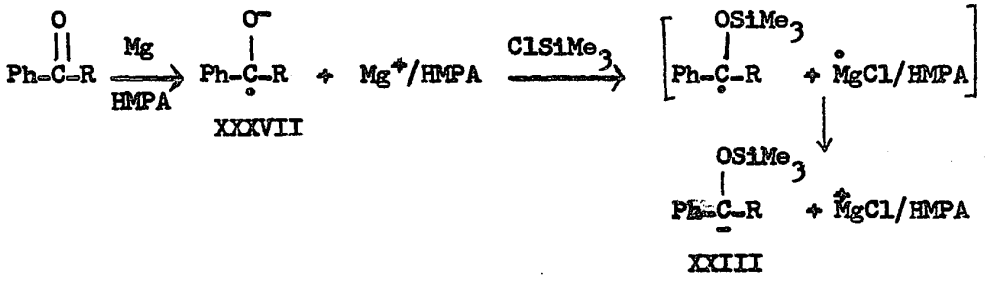
<u>With acetophenone</u>:

The reaction of chlorotrimethylsilane and magnesium in hexamethylphosphoramide with acetophenone yielded a mixture of meso and dl 2,3-diphenyl-2,3-bis(trimethylsiloxy)butane (XXXVI) in 88% yield.



Compound XXXVI can be hydrolyzed to the corresponding pinacol. The reaction mixture did not turn intense blue as was the case with benzaldehyde and benzophenone, but,instead, remained clear yellow all the time. This would seem to indicate that this reaction probably goes via the ionic mechanism rather than the free radical mechanism; although acetophenone reacts with bis(trimethylsilyl)mercury via a free radical route[94] (see p. 50).

At this point it is worth mentioning the mechanism proposed by Calas et al[96] for the reaction of chlorotrimethylsilane and magnesium in hexamethylphosphoramide with aryl aldehydes and ketones. They envisaged the formation of siloxy anion XXIII (Fig. 3) in the following manner:

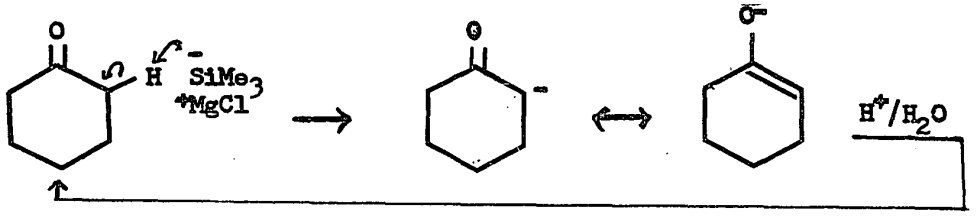


According to this scheme, the anion radical XXXVII is first formed without the necessity of chlorotrimethylsilane. This anion radical should be able to dimerize to give, after hydrolysis, the pinacol.

However, this is different from our experience (p. 44); no reaction at all occurred between benzaldehyde and magnesium in hexamethylphosphoramide without the presence of chlorotrimethylsilane. Therefore, this mechanism is rather doubtful. Since chlorotrimethylsilane is so necessary, it is probably the trimethylsilyl Grignard, or at least some sort of chlorotrimethylsilane-magnesium complex, which is formed first and reacts immediately with the carbonyl compound.

With Cyclohexanone:

Unfortunately only starting materials could be isolated in the reaction of chlorotrimethylsilane and magnesium in hexamethylphosphoramide with cyclohexanone, thus implying that this method of reducing ketones and aldehydes to the corresponding pinacols is not applicable for aliphatic carbonyl compounds. If the silyl Grignard reacts as a free radical, and since aliphatic ketones cannot stabilize a free radical in the same way as aromatic ketones, no reaction takes place. However, Beaumont et al[94] claimed to have reduced cyclohexanone to the pinacol by bis(trimethylsilyl)mercury (see p. 50); whereas Neumann and Neumann[95] found that no reaction occurred between the two compounds (see p. 51). On the other hand, if the ionic mechanism operates in this case, then perhaps the silyl Grignard reacts with cyclohexanone to give the enolate anion which is resonance stabilized and does not react further. After hydrolysis the enolate anion yields only cyclohexanone. Thus,



With 2-furyl methyl ketone:

When chlorotrimethylsilane and magnesium in hexamethylphosphoramide were reacted with 2-furyl methyl ketone, the products decomposed under the reaction conditions and only tars could be isolated. Since 2-furyl methyl ketone has aromatic character, it should have reacted with the reagents used in the same way as the other aromatic ketones; however, less drastic reaction conditions are required.

Summary

When trimethylsilylmethylmagnesium chloride was reacted with aromatic and aliphatic acid chlorides, the corresponding methyl ketones were prepared. In the same way, the reaction of trimethylsilylphenylmethyllithium with benzoyl chloride yielded desoxybenzoin.

Trimethylsilylmethylmagnesium chloride reacted with phthalic anhydride to give a di-γ-lactone (XI), whereas it did not react with succinic anhydride at all, and its reaction with 1,2-cyclobutanedicarboxylic anhydride gave products that could not be identified.

When chlorotrimethylsilane and magnesium in hexamethylphosphoramide were reacted with benzaldehyde and acetophenone, the meso and dl mixtures of the corresponding pinacols were formed; whereas in the reaction with benzophenone, p-benzoyltriphenylmethane was produced. These reagents did not react at all with cyclohexanone, while 2-furyl methyl ketone gave unidentifiable products under the same reaction conditions.

EXPERIMENTAL

The Preparation of Trimethylsilylmethylmagnesium Chloride (IV)

A modified method of Whitmore and Sommer[15] was followed. Magnesium turnings (2.5 g, 0.1 mole), that had been washed previously with dry ether and dried in the dessicator, were placed in a 250-ml three-necked flask and dry ether (50 ml) was added. The flask was equipped with a reflux condenser, an addition funnel, and a magnetic stirring bar, and the system was kept under a nitrogen atmosphere. Then a solution of chloromethyltrimethylsilane (12.2 g, 0.1 mole) in dry ether (25 ml) was placed in the addition funnel. About 5 ml of this silution was added to the magnesium to which a crystal of iodine had been added. When reaction failed to start, the mixture was heated and some of the magnesium turnings were crushed with a stirring rod. The reaction then started, the oil bath was removed, and the solution of chloromethyltrimethylsilane was added over 45 minutes. The reaction mixture was stirred at room temperature for 11 hours and then an aliquot of the Grignard reagent formed was titrated by the method of Gilman.[72] The Grignard was formed in 96% yield and was stored in the refrigerator in a polyethylene bottle fitted with a rubber cap and was kept in a plastic bag filled with nitrogen and calcium chloride. The Grignard reagent was syringed out when required and was retitrated prior to each use. It was found that the titre remained constant over long periods of time.

Determination of the Concentration of Trimethylsilylmethylmagnesium Chloride by the Method of Gilman[72]

An aliquot of the Grignard (~ 1 ml) was added to water in an Erlenmeyer flask and enough standard sulphuric acid (~ 0.2 N) was added to dissolve the magnesium hydroxide produced. The solution was heated at 70-80° prior to back titration with standard sodium hydroxide (~ 0.2 N). Phenolphthalein was used as indicator.

The Preparation of Trimethylsilylphenylmethyllithium (V)

The method of Peterson[17,18] was used. A solution of benzyltrimethylsilane (2.0 g, 12.4 mmole) in dry hexane (2 ml) was added for 15 minutes to a mixture of 2.35 N n-butyllithium (5.3 ml, 12.4 mmole) and tetramethylethylenediamine (1.44 g, 12.4 mmole) under nitrogen at room temperature. The solution turned a purplish red at once. It was stirred for 1 hour more and was used immediately.

The Reaction of Trimethylsilylmethylmagnesium Chloride with Acid Chlorides

The Grignard reagent (IV) was syringed into an addition funnel and added slowly (30-40 minutes) to a solution of the freshly distilled acid chloride in dry ether, under nitrogen, and at room temperature. The reaction mixture was stirred under reflux at 40-45° for 3½ hours. The reaction was followed by VPC analysis. It was then hydrolyzed with dilute aqueous or methanolic hydrochloric acid (~ 1 N) at 40-45°, extracted with ether, and dried over anhydrous magnesium sulphate. The magnesium sulphate was filtered off

and the ether removed on the rotary evaporator to give a residue of the crude product. (See Table 6 for the quantities of reagents used, method of hydrolysis, and yield of crude product.)

TABLE 6

REACTIONS OF TRIMETHYLSILYLMETHYLMAGNESIUM CHLORIDE WITH ACID CHLORIDES

$$Me_3SiCH_2MgCl + RCOCl \longrightarrow RCOCH_3$$

R-	RCOCl g	RCOCl mmoles	Grignard mmoles	Hydrolyzed by	Hydrolyzed for hours	Yield of crude $RCOCH_3$ g
Ph-	1.58	11.0	11	1N HCl	16	1.1
$CH_3(CH_2)_4$-	1.80	13.4	13	1N HCl	16	1.3
m-Cl-C_6H_4-	2.50	14.3	17	1) 1N HCl 2) + MeOH	12 $6\frac{1}{2}$	2.1
$CH_3(CH_2)_8$-	2.3	12	11	1N HCl	13	1.9
C_5H_9-CH_2CH_2-	2.4	15	13	1N HCl	19	1.9
p-Me-C_6H_4-	2.0	13	8	1N HCl/ H_2O-MeOH	11	0.9
p-Cl-C_6H_4-	2.2	13	9	10% HCl (0.5 ml conc. HCl + 4.5 ml MeOH)	16	1.8
C_6H_{11}-	2.0	14	10	10% HCl (1 ml conc. HCl + 2 ml H_2O + 7 ml MeOH)	22	2.0

Characterization of the methyl ketone formed ($RCOCH_3$) and determination of its yield:

Acetophenone (R = Ph)

The NMR spectrum ($CDCl_3$) of the crude product was identical to that of authentic acetophenone; a phenyl multiplet appeared at 1.9-2.6 τ (5 protons) and a singlet at 7.4 τ (3 protons; $-COCH_3$).

The 2,4-dinitrophenylhydrazone of the crude product melted at 244° (lit. 238-40). A mixed melting point with the 2,4-dinitrophenylhydrazone of authentic acetophenone was taken and found to be 244° as well.

VPC analysis of the crude product showed that 85% of it, or 0.9 g, was pure acetophenone, since it had the same retention time as an authentic sample of acetophenone (2 min. at 130° on a UCW98 column). The yield of acetophenone, based on the VPC analysis, was 70%.

2-Heptanone (R = $CH_3(CH_2)_4$)

VPC analysis (UCW98 column) of the crude product showed that 46% of it was a fraction that had a retention time of 3 minutes at 100°. The crude product was distilled and the fraction that was collected (0.4 g) at 155-9° (lit. b.p. for 2-heptanone is 151°) had the same retention time for its largest peak.

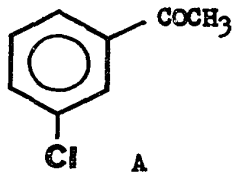
The NMR spectrum (neat) of the distilled product showed a singlet at 7.4 τ (3 protons; $-COCH_3$), a triplet at 7.2 τ (2 protons; $-CH_2\underline{CH_2}CO-$), and a complex multiplet at 8.0-8.6 τ (9 protons; aliphatic protons).

The 2,4-dinitrophenylhydrazone of the distilled product melted at 88-90° (lit. 89° for 2-heptanone).

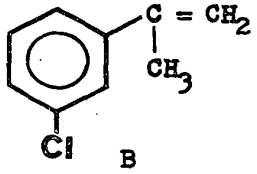
The yield of 2-heptanone, based on the VPC analysis, was 46%.

<u>meta-Chloroacetophenone (R = m-Cl-C_6H_4)</u>

The NMR spectrum ($CDCl_3$) of the crude product showed that it was a mixture of m-chloroacetophenone (A) and 1-methyl-1-(3')-chlorophenylethylene (B) in the ratio of ~2:1. There was a phenyl multiplet at 1.9-2.7 τ, two singlets at 7.4 and 7.8 τ in the ratio of ~2:1 (an acyl and a vinylic methyl group, respectively), and two singlets at 4.6 and 4.8 τ (two different vinylic protons). There was also a relatively small singlet at 9.8 τ (silyated compound).



A



B

The VPC analysis of the crude product (UCW98 column, 110-250° at 20°/min.) showed three compounds to be present. The first had a retention time of 3.5 minutes, came over at 180°, and represented 30.4% of the total yield. This was compound B. The second had a retention time of 4 minutes, came over at 190°, and represented 51.5% of the total yield. This was compound A. The third, the silylated compound, had a retention time of 6.4 minutes, came over at 240°, and represented 11% of the total yield. Thus, the percent yield of compound A, based on VPC analysis, was 50%, while that of compound B was 29%.

The crude product was distilled and four fractions were collected. The ratio of compound A to compound B in each fraction was determined by NMR ($CDCl_3$) and VPC analysis. The results are tabulated in Table 7. The oxime of fraction four melted at 85-6° (lit. 88°).

TABLE 7

RATIO OF COMPOUND A TO COMPOUND B IN THE FRACTIONS COLLECTED BY THE DISTILLATION OF CRUDE META-CHLOROACETOPHENONE

Fraction no.	b.p. range (°C)	Weight (g)	Ratio A:B by NMR	Ratio A:B by VPC	%A (average)
1	124-132	0.32	0.87	0.95	47
2	132-138	0.16	2.1	1.4	63
3	138-142	0.19	6.4	3.8	84
4	145-160	0.46	15.1	12.4	93

2-Undecanone ($R = CH_3(CH_2)_8$)

2-Undecanone decomposed on the VPC column, so that form of analysis could not be used in this case. The crude product was analyzed by NMR (neat) to be a mixture of 2-undecanone and decanoic acid in a 1:1 molar ratio. Since their molecular weights are almost the same (170, 172 respectively), their ratio by weight is also 1:1. The NMR data follows:

τ value	multiplicity	integration # squares	# protons	assignment
-2.2	broad singlet	2.5	1	-COOH

τ value	multiplicity	integration # squares	# protons	assignment
7.7	triplet	10	4	RCH_2CH_2-CO-
8.0	singlet	7.5	3	$-CO-CH_3$
8.7-9.2	multiplet	85	34	$CH_3(CH_2)_7-R$ same as for $CH_3(CH_2)_7CH_2COCl$

Therefore, the yield of 2-undecanone, based on the analysis of the NMR spectrum, is 0.95 g which is a 52% yield.

The crude product was washed with a 10% sodium hydroxide solution several times. The basic washings were reacidified and extracted with ether to yield 0.70 g of decanoic acid: mp 31-2°(lit. 31.6°); NMR spectrum (CCl_4) showed a singlet at -2.2 τ (1 proton), a triplet at 7.7 τ (2 protons), and a multiplet at 8.7-9.2 τ (17 protons). All the signals were sharp. The ether layer yielded 0.72 g of fairly pure 2-undecanone: NMR spectrum (CCl_4) showed a triplet at 7.7 τ (2 protons), a singlet at 8.0 τ (3 protons), and a multiplet at 8.7-9.2 τ (17 protons). But the signals were not very sharp.

The 2-undecanone so isolated was redistilled yielding 0.53 g of pure compound (bp 98-100°/9-10 mm) whose NMR spectrum (CCl_4) gave much sharper signals at the same positions and in the same ratios as previously. The 2,4-dinitrophenylhydrazone of the redistilled product melted at 62-3° (lit. 63°).

1-Cyclopentylbutane-3-one (R = $C_5H_9-CH_2CH_2$)

The ether extract of the reaction mixture, after hydrolysis, was concentrated, taken up in 15 ml of 7% sodium bicarbonate solution,

then extracted with ether to yield 1.9 g of crude product. This product decomposed on the VPC column.

The basic aqueous layer was reacidified and extracted with ether to yield 0.1 g of 3-cyclopentylpropanoic acid: NMR (CCl_4) showed a singlet at -1.9 τ (1 proton; -COOH), a triplet at 7.7 τ (2 protons; RCH_2-CH_2-COOH), and a multiplet at 8.1-9.1 τ (11 protons; $C_5H_9-CH_2-R$).

The crude product gave the following NMR data (neat):

τ value	multiplicity	integration # squares	# protons	assignment
-1.9	broad singlet	1	0.2	-COOH
7.7	triplet	10	2.3	RCH_2-CH_2-CO-
8.0	singlet	13	3	$-COCH_3$
8.1-9.1	multiplet	57	13	$C_5H_9-CH_2-R$

The product seems to be a mixture of 1-cyclopentylbutane-3-one and 3-cyclopentylpropanoic acid in the ratio of 2:0.3 (from the 7.7 τ signal) or 11:2 (from the 8.1-9.1 τ signal) and the fraction of the methyl ketone is 2/2.3 = 0.87 or 11/13 = 0.85, respectively. Since the molecular weights of the ketone and the acid are almost the same (140,142 respectively), the molar ratio also represents the ratio by weight. Thus the yield of 1-cyclopentylbutane-3-one is 1.6 g which is an 85% yield.

The crude methyl ketone was distilled and 1.2 g were collected at 75-77°/7 mm. Its elemental analysis was found to be C = 76.9%, H = 11.5%; the calculated values were C = 77.1%, H = 11.5%. The 2,4-dinitrophenylhydrazone of the distilled product melted at 87.5-88°.

1-Cyclopentylbutane-3-one was found not to have ever been made before and so this is a new compound.

para-Methylacetophenone (R = p-Me-C_6H_4)

The ether extract of the reaction mixture was washed with a 5% sodium hydroxide solution. The basic washings were reacidified and extracted with ether to yield 0.23 g of p-toluic acid, which melted at 176-9° (lit. 179-80°).

The ether layer yielded 0.9 g of crude p-methylacetophenone. Its NMR spectrum (neat) showed an AB quartet at 2.4-3.4 τ (5 protons; p-substituted benzene ring), a singlet at 7.9 τ (3 protons; CH_3-Ph), and a singlet at 8.1 τ (3 protons; $-COCH_3$). Its 2,4-dinitrophenylhydrazine derivative melted at 258-9° (lit. 258°). VPC analysis (UCW98 column; 130° for first 5 minutes, then 130-230° at 20°/min.) indicated that 87% of it (0.6 g) was p-methylacetophenone (retention time 3.5 minutes). Thus the yield of p-methylacetophenone was 73%.

para-Chloroacetophenone (R = p-Cl-C_6H_4)

When the ether extract of the reaction mixture was shaken with a 5% sodium hydroxide solution, 0.2 g of p-chlorobenzoic acid precipitated out. The mixture was reacidified and extracted with ether to yield 1.8 g of residue. When this residue was dissolved in carbon tetrachloride, more crystals of the acid precipitated out (0.3 g). The melting point of the precipitated crystals was 177-83°; authentic p-chlorobenzoic acid, prepared by the acid hydrolysis of p-chlorobenzoyl chloride, melted at 182-4°. Their IR spectra (KBr) were identical.

The IR spectrum (film) of the 1.5 g of residue left showed the presence of the methyl ester of p-chlorobenzoic acid; absorptions in cm^{-1} at 1720 ($>C=O$ of -COOMe), 1270 (-O-Me of -COOMe), and 1580 (aromatic C = C). The presence of p-chloroacetophenone was also indicated: 1680 ($>C=O$ of R_2CO), 1580 (aromatic C = C). The methyl ester was formed during the acid hydrolysis in methanol of unreacted starting material (p-chlorobenzoyl chloride).

The NMR spectrum (CCl_4) of the residue also showed the presence of the methyl ester of p-chlorobenzoic acid as well as p-chloroacetophenone. The NMR data follows:

τ value	multiplicity	integration # squares	# protons	assignment
2.0-3.0	AB quartet	54	9	$Cl-C_6H_4-CO-$
6.3	singlet	18	3	$-OCH_3$
7.6	singlet	21	3.5	$-COCH_3$

The molar ratio of p-chloroacetophenone to methyl-p-chlorobenzoate is 3.5:3 and the molar fraction of p-chloroacetophenone is 3.5/6.5 or 0.54. Since the molecular weights of p-chloroacetophenone and methyl-p-chlorobenzoate are 154 and 170 respectively, the fraction by weight of p-chloroacetophenone is 0.54 x 154/170 or 0.50. The weight of p-chloroacetophenone present in the residue was, therefore, 0.75 g which represented a 55% yield.

A mixture of acetophenone (0.48 g, 4 mmole) and methyl benzoate (0.34 g, 2.5 mmole) was made up. The IR spectrum (film) of this mixture was similar to that of the residue above. The NMR spectrum (neat) showed the ratio of the acyl group to the methoxy group to be

4:2.5, which is the ratio in which the mixture was made up. Therefore, this is a valid method for determining the fraction of ketone present in the mixture, as was used above for p-chloroacetophenone.

The 2,4-dinitrophenylhydrazine derivative of the mixture of acetophenone and methyl benzoate melted at 240-2°. The literature value for the melting point of acetophenone-2,4-dinitrophenylhydrazone is 242°. Therefore, in this mixture only the ketone formed a hydrazone; the methyl ester did not. The 2,4-dinitrophenylhydrazine derivative of the above residue melted at 230-1° (lit. value for p-chloroacetophenone-2,4-dinitrophenylhydrazone is 231°).

Cyclohexyl methyl ketone (R = C_6H_{11})

The ether extract of the hydrolyzed reaction mixture was washed with a 5% sodium hydroxide solution. The ether layer yielded 2.0 g of residue. The IR spectrum (film) of this residue showed the presence of the methyl ester of cyclohexane carboxylic acid: absorptions in cm^{-1} at 1730 (> C=O of -COOMe) and 1250 (-C-Me of -COOMe). Cyclohexyl methyl ketone was also present: absorption at 1710 (> C=O of R_2CO). The methyl ester was formed during the acid hydrolysis in methanol of unreacted cyclohexane carbonyl chloride.

The NMR spectrum (CCl_4) of the residue also showed the presence of the methyl ester: a singlet at 6.2 τ ($-OCH_3$). It also indicated that the methyl ketone was present: a singlet at 7.7 τ ($-COCH_3$). The ratio of the acyl to the methoxy group could not be determined from the NMR spectrum because the cyclohexyl protons (7.3-8.6 τ multiplet) interfered with the integration of the singlet at 7.7 τ.

So the yield was determined by making the 2,4-dinitrophenylhydrazine derivative of the total amount of residue. A quantity of 2.2 g was isolated which melted at 132-8° (lit. value for cyclohexyl methyl ketone-2,4-dinitrophenylhydrazone is 140°). Thus the yield of cyclohexyl methyl ketone was 0.9 g which was a 71% yield.

The Reaction of Trimethylsilylphenylmethyllithium (V) with Benzoyl Chloride

A freshly prepared solution of trimethylsilylphenylmethyllithium (V) (12.4 mmoles) was transferred via syringe into an addition funnel which had been flushed with nitrogen, and it was added slowly (1½ hours) to redistilled benzoyl chloride (2.3 g, 16.4 mmoles). The solution was stirred at room temperature for 2 hours. A yellowish precipitate of lithium chloride came out during the course of the reaction. A solution of concentrated aqueous ammonium chloride (7 ml) was added to the reaction mixture and it was stirred at room temperature for 22 hours. It was then extracted with ether, washed with a 7% sodium hydroxide solution, and dried over anhydrous magnesium sulphate to yield a semi-crystalline material (3.1 g) which, when dissolved in carbon tetrachloride, precipitated out crystals of benzoic acid (0.1 g), mp 123-5° (lit. 122.4°).

VPC analysis (LAC728 column; 100-215° at 20°/min.) of the remaining residue indicated the presence of benzyltrimethylsilane (retention time of 2 minutes), desoxybenzoin (retention time of 16 minutes), and benzoic acid (retention time of 20 minutes).

The NMR spectrum (CCl_4) of the residue gave the following data:

τ value	multiplicity	integration # squares	# protons	assignment
2.8	multiplet	60	30	Phenyl protons
5.8	singlet	4	2	$Ph-\underline{CH_2}-COPh$
8.0	singlet	4	2	$Ph-\underline{CH_2}-SiMe_3$
9.9	singlet	40	20	$\underline{Me_3}SiOSi\underline{Me_3}$
10.0	singlet			$PhCH_2-Si\underline{Me_3}$

For desoxybenzoin, the two methylenic protons at 5.8τ are represented by four squares in the integration. Therefore, twenty of the sixty squares for the phenyl protons at 2.8τ represent the ten phenyl protons of desoxybenzoin. Thus, about one-third of the residue is desoxybenzoin. The yield of desoxybenzoin is, therefore, about 1 g, which is a 45% yield.

The Reaction of Trimethylsilylmethylmagnesium Chloride (IV) with Phthalic Anhydride

Trimethylsilylmethylmagnesium chloride (5.5 ml of 1.77N, 9.7 mmoles) was added slowly (30 minutes), with stirring, to resublimed phthalic anhydride (1.84 g, 12.4 mmoles) in 1,2-dimethoxyethane (10 ml) under nitrogen. The mixture was stirred for 21 hours at 60°. It was then hydrolyzed with 1N hydrochloric acid (12 ml) for 12 hours, extracted with ether, and dried over anhydrous magnesium sulphate. When the ether extract was concentrated, a white precipitate came out (0.37 g) which melted at 168-9°. After evaporation of the solvents there was left a semi-crystalline whitish material (1.93 g) which was recrystallized from carbon tetrachloride to yield a white

solid (0.86 g) which melted at 152-7°. The IR and NMR spectra of this compound were identical to those of the first precipitate which melted at 168-9°, but it was not as pure. The product was identified as the γ-lactone (XI) and was isolated in 63% yield. (The structure is shown on p. 36).

Proof of structure of compound XI:

IR spectrum (KBr): Bands at cm^{-1} 3360 and 1740 represented the stretching frequencies of an OH group and of the C=O group, respectively, of a γ-lactone. There was no acidic -OH stretching in the 3000-2500 cm^{-1} region and no other carbonyl stretching was seen (ie. no anhydride, acid, or ketone). The C=C aromatic stretching was present at 1600 cm^{-1} as well as the aromatic C-H bending band of a 1,2-disubstituted benzene ring at 730 cm^{-1}. (See Fig. 6).

Mass spectrum: The molecular ion had an m/e of 312 which corresponds to the molecular weight of compound XI. The major fragment ions had m/e of 294, 267, 173, 164, 149 (the base peak), and 146. (Fig. 4). The fragmentation pattern of compound XI leading to these ions is shown in Fig. 5.

Fig. 4

The Mass Spectrum of Compound XI

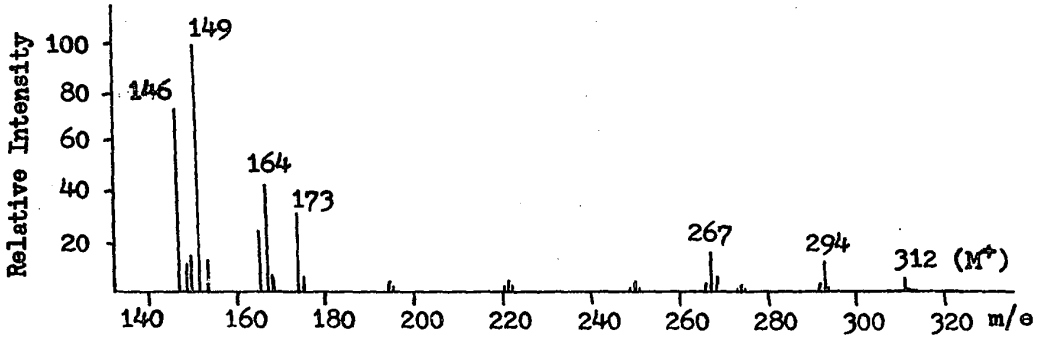


Fig. 5

The Mass Spectral Fragmentation Pattern of Compound XI

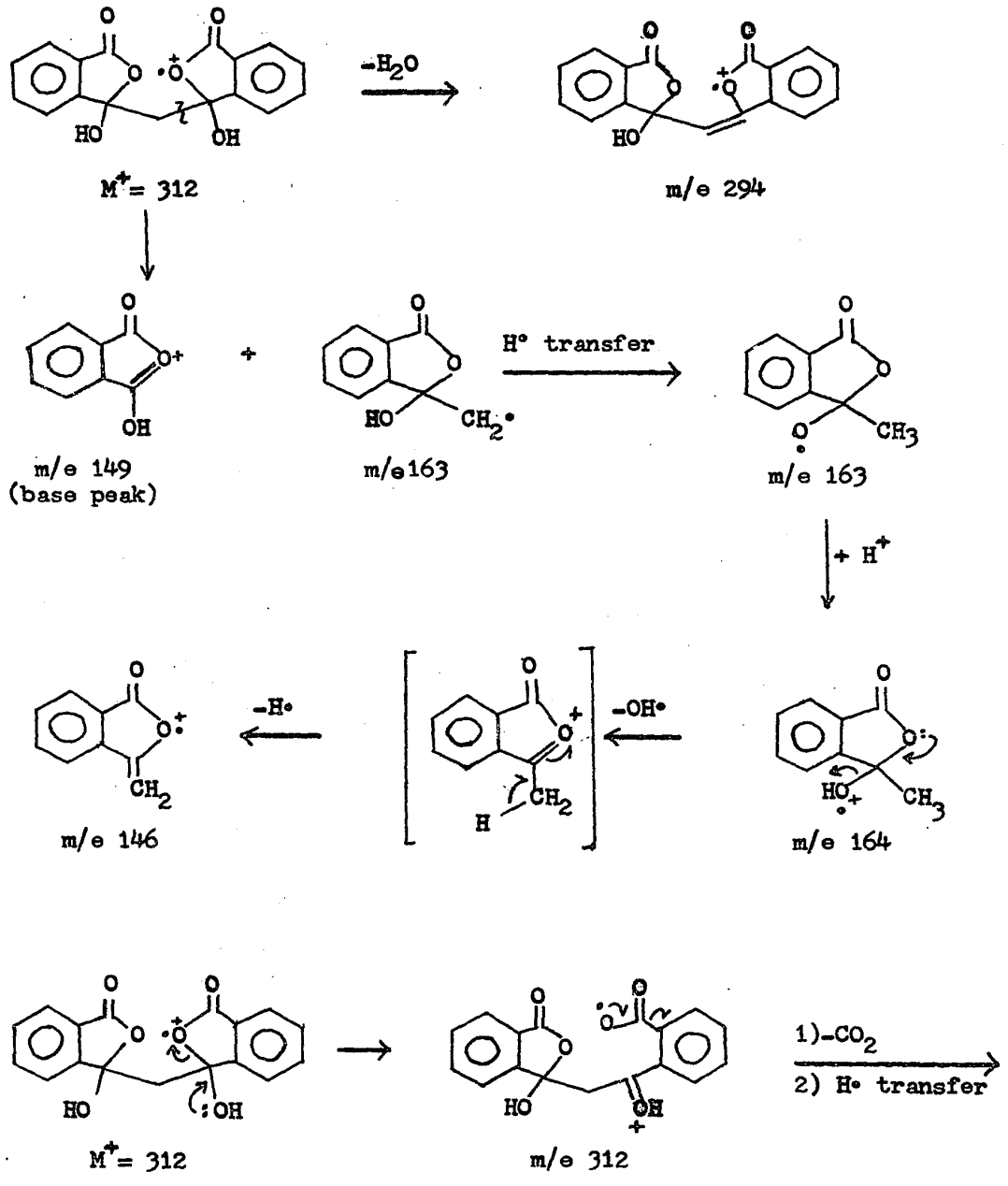
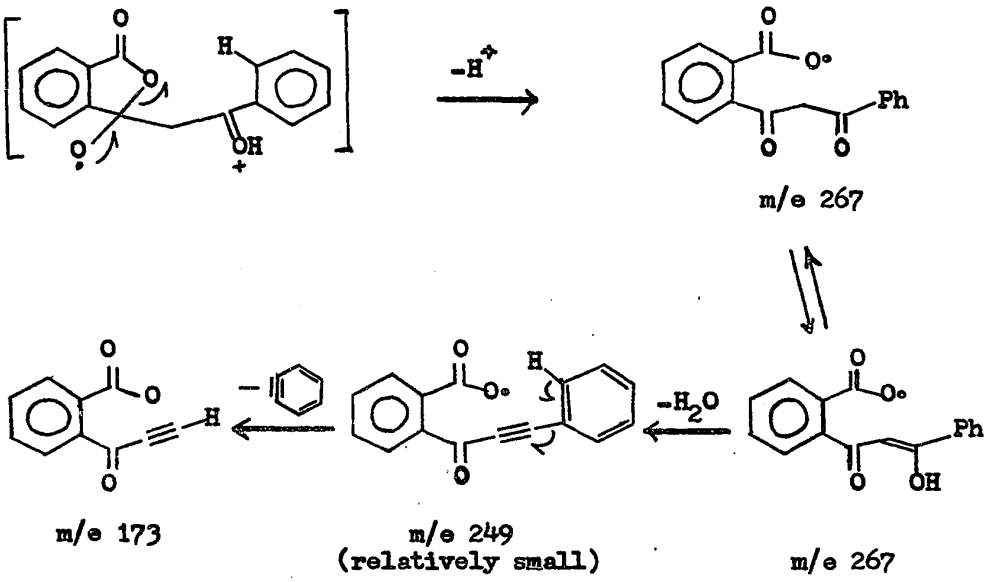


Fig. 5 continued



Elemental analysis: The carbon and hydrogen analysis of compound XI compared favourably with the calculated values: found carbon 65.3 %, hydrogen 3.8 %; calculated carbon 65.4 %, hydrogen 3.9 %.

NMR spectrum (CF_3COOH): There was a ten proton multiplet at 2.4-2.9 τ and a two proton singlet at 6.7 τ. Both the phenyl protons and the hydroxy protons resonate in the 2.4-2.9 τ region, whereas the methylenic protons resonate at 6.7 τ. (See Fig. 7).

UV spectrum (95% EtOH; c = 7.7×10^{-5} M): The following absorption bands were seen:

λmax (mμ)	absorption coefficient (ε)	assignment
212	10,500	primary aromatic band
232	7930	secondary aromatic band
325	2600	carbonyl of conjugated ester

Fig. 6

IR Spectrum of Compound XI

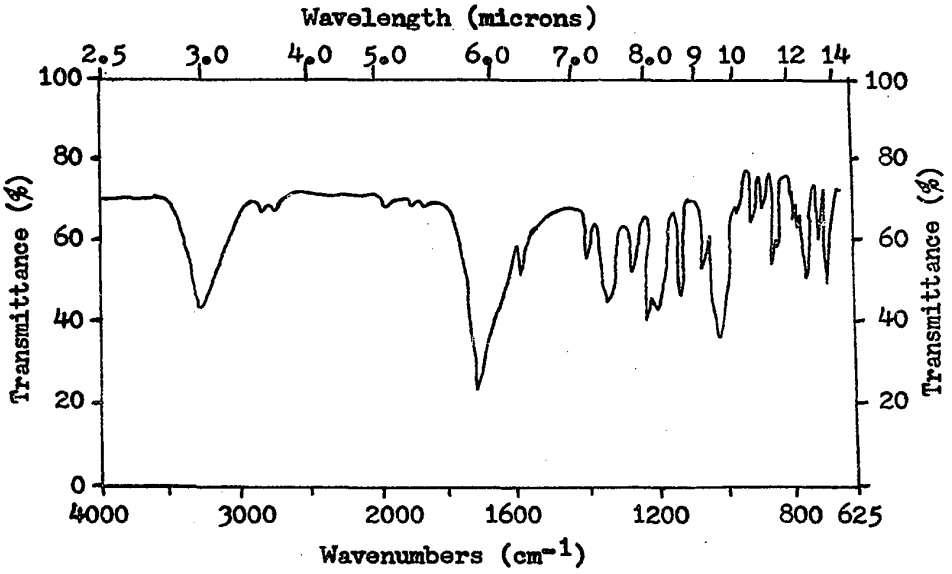
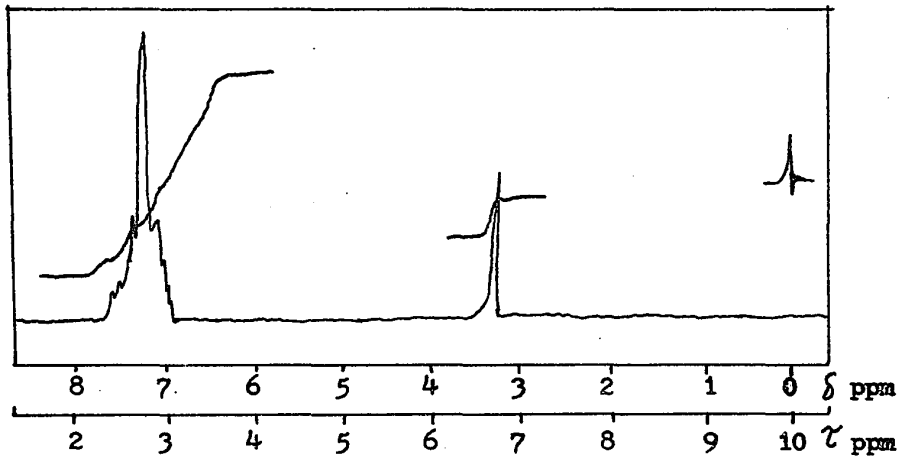
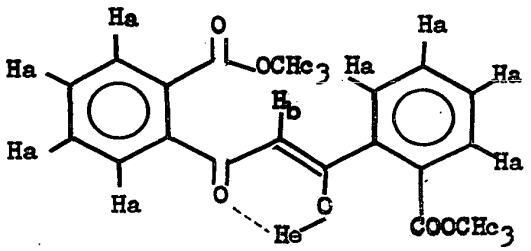


Fig. 7

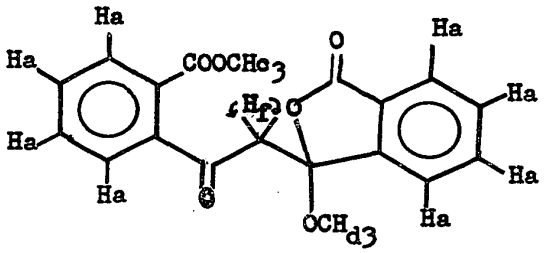
NMR Spectrum of Compound XI



Derivatives: Compound XI was methylated with excess methanol and hydrogen chloride gas. The derivative formed was a mixture of methyl esters XXXVIII and XXXIX in a 1:1 molar ratio as indicated by its NMR, IR, and mass spectral data.



XXXVIII

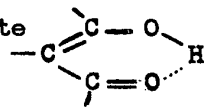


XXXIX

The NMR (CCl_4) spectral data was as follows:

τ value	multiplicity	integration # squares	# protons	assignment
2.50	multiplet	87	16	phenyl protons (Ha)
3.95	singlet	6	1	vinylic proton (H_b)
6.18	singlet	42	9	$-OCH_3$ (Hc)
6.25	singlet	14	3	$-OCH_3$ (H_d)
6.35	singlet	6	1	-OH (He)
7.05	singlet	10	2	$-CO-\underline{CH_2}-\overset{|}{\underset{|}{C}}=O$ (H_f)

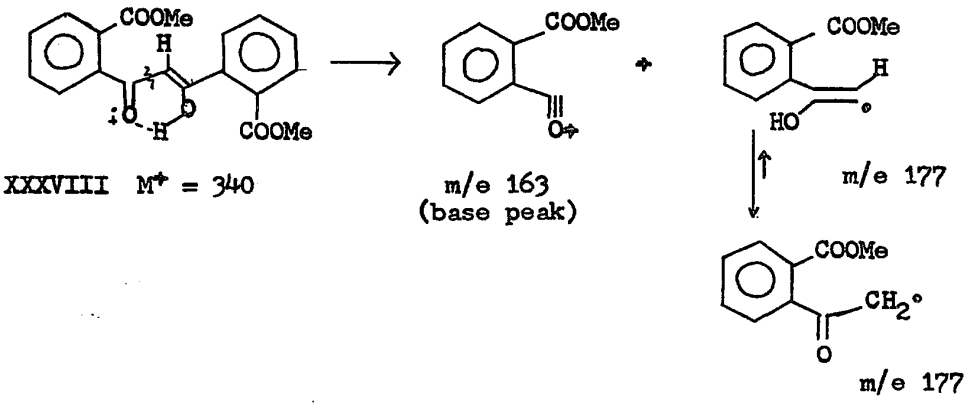
This data fits structures XXXVIII and XXXIX in a 1:1 molar ratio.

The IR spectrum (CCl_4) had bands at cm^{-1} 1750 (C=O str. of a methyl ester), 1705 (aromatic ketone C=O str.), and at 1600 (conjugated chelate ).

The mass spectrum showed the following: $M^+ = 340$, which is the molecular weight of both compounds XXXVIII and XXXIX; the two largest fragment ions were at m/e 177 and 163. A fragmentation pattern giving rise to these ions is shown in Fig. 8.

Fig. 8

The Mass Spectral Fragmentation Pattern of the Methylated Derivative of Compound XI

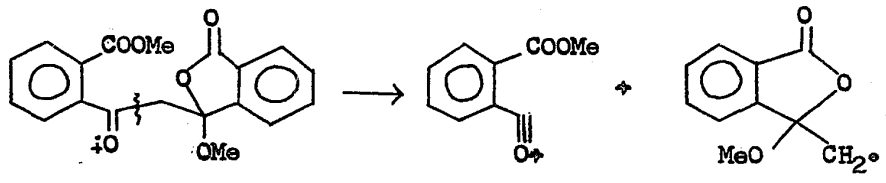


XXXVIII $M^+ = 340$

m/e 163 (base peak)

m/e 177

m/e 177



XXXIX $M^+ = 340$

m/e 163 (base peak)

m/e 177

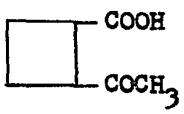
The Attempted Reaction of Trimethylsilylmethylmagnesium Chloride (IV) with Succinic Anhydride

The same procedure was followed as for the reaction with phthalic anhydride. However, the only product that was isolated was succinic acid, mp 155-167° (lit. 182°). The IR and NMR spectra were identical to those of authentic succinic acid. It also formed the same methyl ester as did authentic succinic acid (IR and NMR spectra were identical).

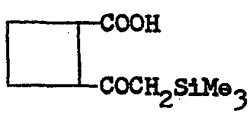
The Attempted Reaction of Trimethylsilylmethylmagnesium Chloride (IV) with cis-1,2-Cyclobutanedicarboxylic Anhydride

The same procedure was followed as for the reaction with phthalic anhydride. However, a mixture of products was formed that could not be positively identified. A small yield of cis-1,2-cyclobutanedicarboxylic acid was formed. It was identified by comparison of its melting point, IR, and NMR spectra with those of authentic sample.

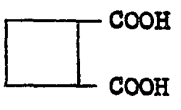
The NMR spectrum ($CDCl_3$) of the mixture of products showed the following: a singlet at -1.8τ (-COOH), a singlet at 4.3 τ (vinylic protons), a singlet at 6.1 τ (acyl group), a multiplet at 6.4 τ and at 7.5 τ (cyclobutane ring protons), a small singlet at 8.5 τ (α-silyl protons), and a singlet at 9.8 τ (trimethylsilyl group). From this data there seemed to be a mixture of compounds XL, XLI, XLII, and XLIII present.



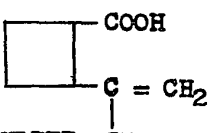
XL



XLI



XLII



XLIII

The IR spectrum ($CHCl_3$) also indicated the presence of a carboxylic acid (broad band at 3200-2500 cm^{-1}) as well as several carbonyl groups (1740, 1720 cm^{-1}).

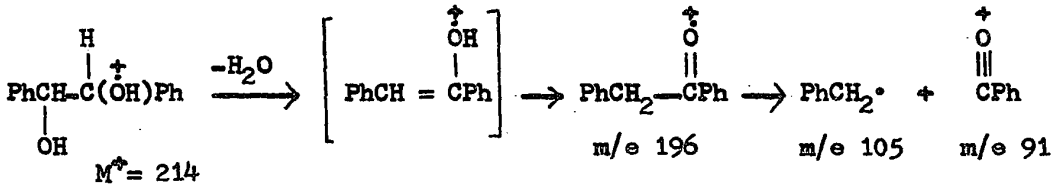
A small amount of the residual oil was separated by preparative TLC (solvent, EtOAc). The largest band, visualized by short wave UV light, was isolated at R_f = 0.8. The carboxylic acid and vinylic protons were gone in the NMR spectrum, but the IR spectrum indicated the presence of a carboxylic acid. It also showed that a carbonyl group was still present (1680 cm^{-1}) as well as the Si-O linkage (1100 cm^{-1}; strong band).

The mass spectrum indicated that the molecular weight was 215 which does not fit any of the above compounds. Compound XLI has a molecular weight of 214. The other fragment ions in the spectrum had m/e of 201, 199,198, 185, 171, 157, 155, 154, 143, 140, 127, 99, 89, 82, 81, 75, and 73. No structures could be thought of that would fragment to give the above ions.

The Attempted Preparation of Bis(trimethylsilyl)phenylmethane

The method of Calas et al[59] was followed. Magnesium turnings (4.8 g, 0.2 mole) were suspended in a solution of redistilled chlorotrimethylsilane (52.4 g, 0.5 mole) in hexamethylphosphoramide (70 ml) under nitrogen. After preheating the mixture to 100-110°, a solution of redistilled benzaldehyde (10.4 g, 0.1 mole) in hexamethylphosphoramide (40 ml) was added gradually (1 hour). After addition was complete, the mixture was stirred at 95° for 75 hours. It turned a blue-black colour by that time. The unreacted magnesium

was filtered off, the solution was hydrolyzed with saturated aqueous ammonium chloride solution, and extracted with ether, yielding a semi-crystalline yellow residue (14 g) which still contained some hexamethylphosphoramide (doublet at 7.1τ in the NMR spectrum). So the residue was taken up in excess water and extracted with ether to yield a semi-crystalline material (10.5 g). When this was dissolved in carbon tetrachloride, meso 1,2-diphenylethane-1,2-diol precipitated out (1.71 g); mp 134-134.5° (lit. 137-8°). The NMR spectrum ($CDCl_3$) showed a singlet at 2.4τ (5 protons; phenyl protons), a singlet at 4.8 τ (1 proton; PhC<u>H</u><), and a broad signal at 7.5 τ (1 proton; -OH). The IR spectrum (KBr) had bands at cm^{-1}, 3300-3400 (-OH stretching, H-bonded), 1030, 1040 (-OH bending), 760, 710, and pattern in 5-6 μ region (monosubstituted benzene ring), 1500 (aromatic C=C), 2900 single sharp peak (~ C-H). The mass spectrum showed that the molecular weight was 214, and the major fragment ions had m/e of 196, 105, and 91, which arise as follows.



Another 7.1 g of a mixture of meso and dl 1,2-diphenylethane-1,2-diol was recrystallized from the oil; mp 92-93 (lit. meso 137-8°, dl 117-8°). The NMR data ($CDCl_3$) of this mixture was as follows:

τ value	multiplicity	integration # squares	# protons	assignment
2.4	multiplet	64	18	Phenyl protons (meso and dl)

τ value	multiplicity	integration # squares	# protons	assignment
4.85	singlet	3.5	1	PhCHOH-CHOHPh (meso)
5.05	singlet	8	2	PhCHOH-CHOHPh (dl)
6.5	singlet	10	3	PhCHOH-CHOHPh (meso and dl)

From these data, the ratio of meso to dl form in the mixture was 1:2. The IR spectrum (KBr) and the mass spectrum of this mixture were identical to those of the pure meso form.

The total yield of 1,2-diphenylethane-1,2-diol (meso and dl) was 8.8 g of which 4.05 g was the meso form and 4.75 g was the dl form (dl : meso = 1.17). The total yield was 85%.

The Attempted Pinacolic Reduction of Benzaldehyde by Magnesium in Hexamethylphosphoramide

Magnesium turnings (2.4 g, 0.1 mole) were suspended in hexamethylphosphoramide (70 ml) under nitrogen. After preheating the mixture to 100-110°, a solution of redistilled benzaldehyde (10.2 g, 0.1 mole) in hexamethylphosphoramide (40 ml) was added gradually (45 minutes). After addition was complete, the mixture was stirred at 95-100° for 19 hours. The solution remained clear and all of the magnesium was still present. A 5 ml aliquot was removed and hydrolyzed with 10 ml of 1N hydrochloric acid, and extracted with ether. The ether extracts were washed with water and dried over anhydrous magnesium sulphate. TLC and NMR analyses of the residue obtained showed that only benzaldehyde was present. Therefore, no reaction had taken place.

A few crystals of iodine were added to the above reaction mixture and it was stirred at 95° for another 54 hours under nitrogen. Another 5 ml aliquot was removed and worked up in the same manner. TLC and NMR analysis of the residue obtained still showed the presence of only benzaldehyde.

The Pinacolic Reduction of Benzaldehyde by Chlorotrimethylsilane and Magnesium in Hexamethylphosphoramide

Redistilled chlorotrimethylsilane (10.86 g, 0.1 mole) was added slowly (1 hour) to the above reaction mixture (8.8 g, 0.086 moles of benzaldehyde were still left) and it was stirred under nitrogen at 95° for 22 hours. The solution turned blue-black by that time. The excess magnesium was filtered off and the solution was hydrolyzed with saturated aqueous ammonium chloride solution (100 ml). The solution turned a light brown upon hydrolysis. The solution was still basic, so concentrated hydrochloric acid was added (1 ml) and the solution was extracted with ether. The ether extracts were washed three times with water and dried over anhydrous magnesium sulphate to yield a semi-crystalline residue (10.2 g). A mixture of meso and dl 1,2-diphenylethane-1,2-diol (0.8 g) crystallized out of the residue in carbon tetrachloride; mp 127-9° (lit. meso 137-8°, dl 117-8°). The NMR spectrum ($CDCl_3$) showed that the ratio of meso:dl form was 1:3 (protons resonated at same frequencies as those of 1,2-diphenylethane-1,2-diol in previous reaction). The IR spectrum (KBr) was identical to that of 1,2-diphenylethane-1,2-diol in the previous reaction.

Another 7.1 g of meso and dl 1,2-diphenylethane-1,2-diol crystallized out of the concentrated solution on standing; mp 88-94°. From the NMR spectrum ($CDCl_3$) the ratio of meso:dl form was 11:14.

The total yield of 1,2-diphenylethane-1,2-diol was 7.9 g of which 3.7 g was meso and 4.2 g was dl (dl : meso = 1.13). This was a 90% yield.

The Pinacolic Reduction of Benzophenone by Chlorotrimethylsilane and Magnesium in Hexamethylphosphoramide

Magnesium turnings (0.8 g, 0.033 mole) and benzophenone (9.11 g, 0.05 mole) were placed in a flask which had been evacuated and filled with nitrogen three times. Redistilled hexamethylphosphoramide (30 ml) and a few crystals of iodine were added to the mixture and it was brought to 80°. A solution of chlorotrimethylsilane (4 ml, 0.033 mole) in hexamethylphosphoramide (20 ml) were placed in the addition funnel and a few millilitres of this solution were run into the reaction flask. After a few minutes of stirring the solution turned dark blue. The mixture was then brought to 70° and addition of chlorotrimethylsilane was resumed. During the addition the reaction mixture turned clear yellow again. After addition was complete (45 minutes), the solution turned blue again. It was brought to 60° and stirred for 11 hours more. At the end of that time the solution was blue-black in colour. The unreacted magnesium was filtered off, the solution was hydrolyzed with saturated aqueous ammonium chloride solution (50 ml), and extracted with ether. The ether extracts were washed with three 25 ml portions of water and dried over anhydrous

magnesium sulphate to yield an oily residue (9.20 g) which was taken up in absolute ethanol (15 ml). Upon standing overnight, 2-trimethylsiloxytetraphenylethanol (1.14 g) precipitated out; mp 131-5°. The NMR spectral data was as follows: ($CDCl_3$)

τ value	multiplicity	integration # squares	# protons	assignment
2.9	multiplet	102	20	Phenyl protons
6.9	singlet	5	1	-OH
9.8	singlet	40	8	$-OSiMe_3$

The ratio of the protons at 2.9 : 6.9 : 9.8 τ should have been 20:1:9. The IR spectrum (KBr) had bands at cm^{-1}, 3420 (OH str.), 2860 (aromatic C-H str.), 1440 (aromatic C=C str.), 1380, 1200 (OH bend.), 1050 (O-Si str.), 800 (Si-C str.), 730, 690 (aromatic C-H bending for monosubstituted benzene ring).

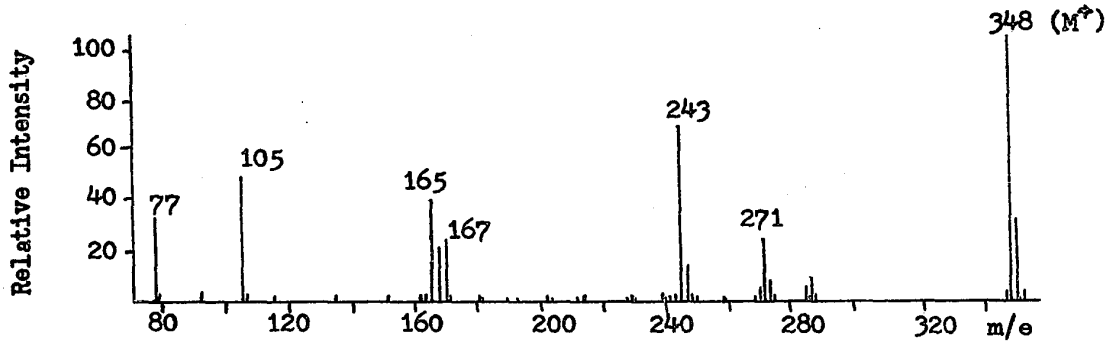
When benzene was added to the crystals, 0.38 g did not dissolve and were filtered off; mp 143-5°. The ratio of protons in the NMR spectrum ($CDCl_3$) for the signals at 2.9 : 6.9 : 9.8 τ was 20:1:9. This was pure 2-trimethylsiloxytetraphenylethanol.

The ethanol was removed from the residue leaving an oil (8.06 g) whose IR spectrum ($CHCl_3$) indicated the presence of a carbonyl group at 1650 cm^{-1}. The residue was recrystallized from 95% ethanol and yielded p-benzoyltriphenylmethane (3.90 g). It was recrystallized twice more from 95% ethanol; mp 142-6°, then at 160-4° (lit.[97] 149-50°, then 163-4°). By using a differential heat calorimeter, the compound was found to have two melting points: there was a small peak at 157° and a larger one at 171.5°. The NMR spectrum ($CDCl_3$)

showed a phenyl multiplet at 2.6 τ (19 protons) and a singlet at 4.2 τ (1 proton; $Ph_3C-\underline{H}$). The IR spectrum (KBr) showed bands at cm^{-1}, 1650 (aromatic ketone C=O str.), 1590 (aromatic C=C str.), 760, 700 (monosubstituted benzene ring), 840 (1,4-disubstituted benzene ring), and a very small band at 3020 (C-H str.). The mass spectrum showed that the molecular weight was 348, and the major fragment ions had m/e of 271, 243, 167, 165, 105, and 77. (Fig. 9). These ions arise as shown in Fig. 10.

Fig. 9

The Mass Spectrum of p-Benzoyltriphenylmethane



The melting point (including mixed melting point), IR, NMR, and mass spectra were all identical to those of authentic p-benzoyltriphenylmethane prepared by the Friedel-Craft reaction[98].

Thus, 2-trimethylsiloxytetraphenylethanol was formed in only 16% yield, while p-benzoyltriphenylmethane was formed in 68% yield.

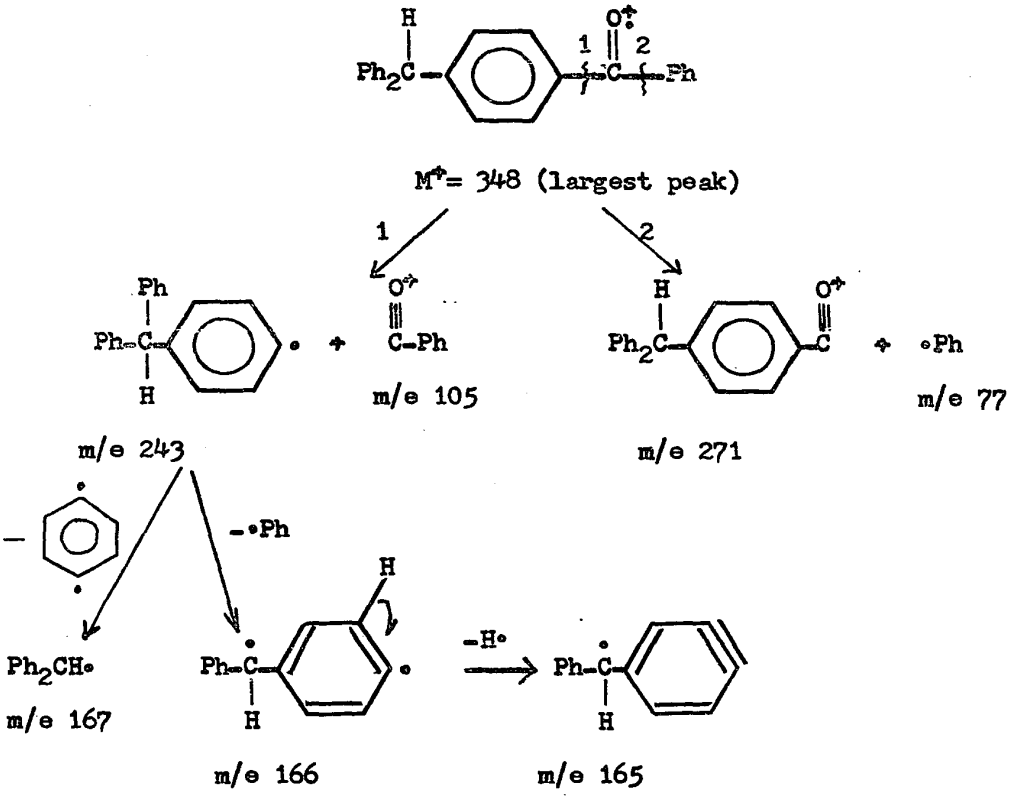
<u>The Preparation of p-Benzoyltriphenylmethane by the Friedel-Craft Reaction</u>[98]

A solution of triphenylmethane (12.2 g, 0.05 mole) and benzoyl chloride (7.7 g, 0.05 mole) in methylene chloride (30 ml) was added,

Fig. 10

The Mass Spectral Fragmentation Pattern

of p-Benzoyltriphenylmethane



with stirring, over 1.5 hours to a suspension of aluminum chloride (6.8 g, 0.05 mole) in methylene chloride (25 ml). The system was kept dry via a calcium chloride drying tube. The solution turned dark red as addition was continued. The mixture was stirred under reflux for another 2.5 hours and then poured into a mixture of ice (100 g) and concentrated hydrochloric acid (100 ml) with vigorous stirring. The solution was then extracted with chloroform to give

a dark brown tarry oil as residue. A resin was formed when absolute ethanol was added to the residue. Upon heating, a large part of the residue went into solution. The reddish-brown solution was cooled and decanted from the resin through a filter paper. The ethanol was removed and the residue was separated by column chromatography (silica gel; eluent benzene). The first fractions collected were a mixture of unreacted triphenylmethane and p-benzoyltriphenylmethane (2.3 g); R_f = 0.60, 0.50, respectively; mp 83-91° (lit. value for triphenylmethane is 94°). So this was mainly triphenylmethane. The fractions collected at R_f = 0.50 were crude p-benzoyltriphenylmethane (4.4 g). This was recrystallized from 95% ethanol three times and compared with the p-benzoyltriphenylmethane formed in the reaction of benzophenone with chlorotrimethylsilane and magnesium in hexamethylphosphoramide. They were identical. The yield of p-benzoyltriphenylmethane in the Friedel-Craft reaction was only 25%.

The Attempted Preparation of p-Benzoyltriphenylmethane by the Reaction of Benzopinacolone with Chlorotrimethylsilane and Magnesium in Hexamethylphosphoramide

Magnesium turnings (0.15 g, 6 mmoles) and chlorotrimethylsilane (1.2 ml, 10 mmoles) were reacted with benzopinacolone (1.74 g, 5 mmoles) in hexamethylphosphoramide in the same way as in the reaction with benzophenone. The reaction mixture turned blue. After work-up, the residue obtained was recrystallized from 95% ethanol yielding yellowish crystals of tetraphenylethylene (0.58 g); mp 217-222° (lit. 223-4°). An exact mass determination on the peak at m/e 332 showed that the best molecular formula was $C_{26}H_{20}$ (ie. tetra-

phenylethylene). The NMR spectrum ($CDCl_3$) showed only a phenyl singlet at 2.5 τ.

TLC analysis (solvent benzene) of the residue showed only one spot having the same R_f value as benzopinacolone (R_f = 0.64). The IR spectrum ($CHCl_3$) was very similar to that of benzopinacolone. In any case, there was no evidence of p-benzoyltriphenylmethane having been formed.

The Pinacolic Reduction of Acetophenone by Chlorotrimethylsilane and Magnesium in Hexamethylphosphoramide

Magnesium turnings (1.2 g, 0.05 mole) and acetophenone (6.01 g, 0.05 mole) were placed in a flask which was evacuated and filled with nitrogen three times. Redistilled hexamethylphosphoramide (30 ml) and a few crystals of iodine were added and the mixture was brought to 78°. Then chlorotrimethylsilane (6 ml, 0.05 mole) in hexamethylphosphoramide (20 ml) were placed in the addition funnel and a few millilitres of this solution were added to the reaction mixture. When no colour change occurred, a few of the magnesium turnings were crushed with a stirring rod. After 20 minutes, when still no colour change had taken place, the rest of the chlorotrimethylsilane solution was added over 30 minutes. The temperature was brought down to 60° and the mixture was stirred for 12 hours, but still no colour change had taken place. The temperature was raised to 86° and the mixture was stirred for another 12 hours, but the reaction mixture was still clear. The temperature was raised to 100° and the mixture was stirred for a further 12 hours at which point the mixture took

on a yellow colour. Stirring was continued at 92° for another 33 hours (total reaction time was 69 hours).

The reaction mixture was then cooled, the unreacted magnesium was filtered off, and the solution was hydrolyzed with saturated aqueous ammonium chloride solution and extracted with chloroform. The chloroform extracts were washed four times with water and dried over anhydrous magnesium sulphate to yield a residue (43.19 g) which was mainly hexamethylphosphoramide. So the residue was taken up in excess water and extracted with ether. The ether extracts were dried over anhydrous magnesium sulphate and yielded 10.42 g of residue. This was recrystallized from 95% ethanol to yield 3.57 g of a mixture of meso and dl 2,3-diphenyl-2,3-bis(trimethylsiloxy)butane; mp 93-103°. The IR spectrum showed bands at cm^{-1}, 2960, 2880 (C-H str.), 1440, 1365 (C-H bending), 1490 (aromatic C=C str.), 1250 ($Si-CH_3$ sym. deformation), 850, 768 ($-SiMe_3$ rocking), 1140 (Si-O-C str.), 700, 768 (C-H bending in monosubstituted benzene ring). The NMR ($CDCl_3$) spectral data was as follows:

τ value	multiplicity	integration # squares	# protons	assignment
2.4	multiplet	77	12	$(PhCH_3OSiMe_3C)_2$ (meso and dl)
8.05	singlet	6.5	1	$(PhCH_3OSiMe_3C)_2$ (form 1)
8.40	singlet	39	6	$(PhCH_3OSiMe_3C)_2$ (form 2)
9.9	singlet	19	3	$(PhCH_3OSiMe_3C)_2$ (form 1)
10.0	singlet	115	18	$(PhCH_3OSiMe_3C)_2$ (form 2)

The ratio of form 2 : form 1 was 6:1 (86% form 2). The mass spectrum showed that the molecular ion had m/e of 386, and the major fragment ions were at m/e 371,281, 193 (base peak), and 73; there were some less important ions at m/e 177, 163, 147, 135, 105, 103, and 91. (Fig. 11). The major ions arise as follows:

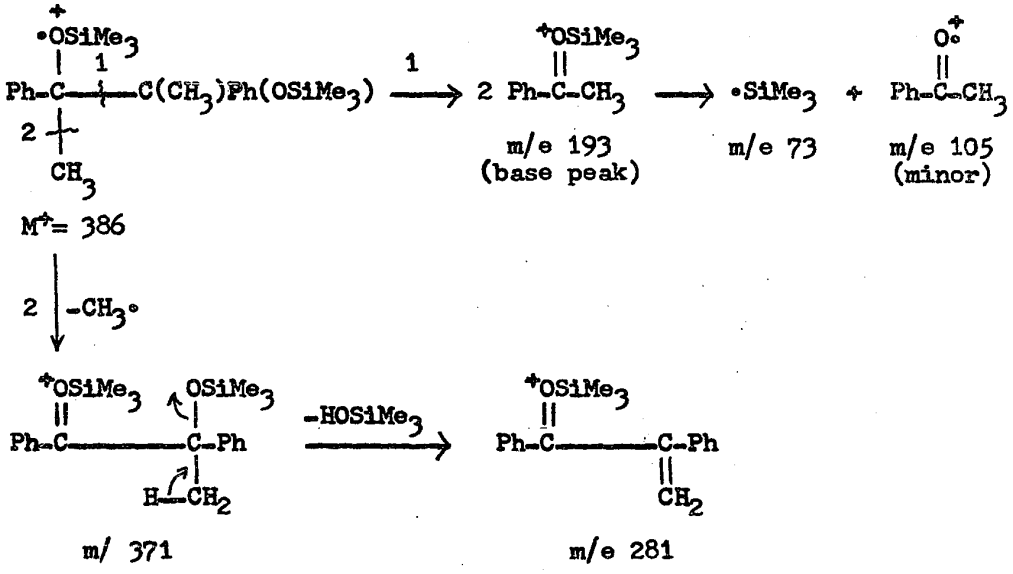
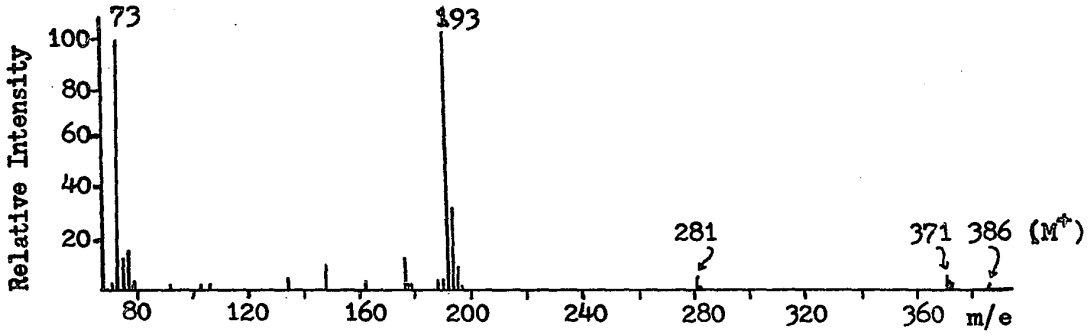


Fig. 11

The Mass Spectrum of 2,3-Diphenyl-2,3-bis(trimethylsiloxy)butane



Determination of whether form 2 was meso or dl:

The above mixture of meso and dl 2,3-diphenyl-2,3-bis(trimethylsiloxy)butane was recrystallized twice from absolute ethanol to yield 1.72 g of crystals which melted at 109-111°. The NMR spectrum ($CDCl_3$) showed that this was only form 2: there was a phenyl multiplet at 2.4 τ (10 protons), a singlet at 8.40 τ (6 protons; $(PhCH_3OSiMe_3C)_2$ of form 2), and a singlet at 10.0 τ (18 protons; $(PhCH_3OSiMe_3C)_2$ of form 2). Elemental analysis of the recrystallized product gave good results: found carbon = 68.1%, hydrogen = 8.8%; calculated carbon = 68.3%, hydrogen = 8.9% for molecular formula $C_{22}H_{34}O_2Si_2$.

A quantity of 125 mg of the recrystallized form 2 was hydrolyzed with 16 ml of 0.6N hydrochloric acid in 5 ml of dioxane and a drop of chloroform, by stirring for 6 hours at room temperature followed by 17 hours at 65°. The solution was then diluted with water, extracted with chloroform, and dried over anhydrous magnesium sulphate. The residue so obtained was separated by preparative TLC (solvent benzene) and the band at R_f = 0.35 was collected (50 mg, 67% yield) by extracting with a chloroform-methanol solution. The product melted at 108-112° (lit. mp of meso 2,3-diphenylbutane-2,3-diol is 117-8°). The NMR spectrum ($CDCl_3$) of this product showed a phenyl singlet at 2.66 τ (10 protons), a singlet at 8.41 τ (6 protons; $(PhCH_3OHC)_2$ meso form), and a singlet at 7.70 τ which disappeared when exchanged with deuterium oxide (2 protons; -OH). By comparison of this spectrum with published[99] NMR data on meso and dl 2,3-diphenylbutane-2,3-diol in deuterochloroform (Fig. 12), it was confirmed that form 2 was the meso form.

Fig. 12

NMR Spectra of meso and dl 2,3-Diphenylbutane-2,3-diol in Deuterochloroform[99]

meso		dl	
Description of proton	Resonance frequency (τ)	Description of proton	Resonance frequency (τ)
$-CH_3$	8.45	$-CH_3$	8.55
-OH	7.70	-OH	7.32
-Ph	2.83	-Ph	2.83

After the first batch of crystals of 2,3-diphenyl-2,3-bis(trimethylsiloxy)butane (86% meso or form 2) had crystallized out, there was left 6.85 g of residual oil whose NMR spectrum ($CDCl_3$) showed that it was mainly (93%) 2,3-diphenyl-2,3-bis(trimethylsiloxy)butane (meso and dl).

So the residue was separated by column chromatography (silica gel; eluent benzene) and the fractions having an R_f value of 0.70 were collected to yield 4.93 g of a yellow oil. This was recrystallized from 95% ethanol to give 0.52 g of crystals melting at 77-97° whose NMR spectrum ($CDCl_3$) indicated that it was a mixture of 65% meso and 35% dl 2,3-diphenyl-2,3-bis(trimethylsiloxy)butane.

Another 0.17 g of crystals came out upon standing. They melted at 89-100° and their NMR spectrum ($CDCl_3$) indicated that this mixture consisted of 72% meso and 28% dl form of 2,3-diphenyl-2,3-bis(trimethylsiloxy)butane.

The NMR spectrum ($CDCl_3$) of the mother liquors (4.24 g) indicated that it contained 85% dl and 15% meso 2,3-diphenyl-2,3-bis(trimethylsiloxy)butane and that it was quite pure (the signals were sharp and in the correct ratio and no other signals were observed). Therefore, the yield of 2,3-diphenyl-2,3-bis(trimethylsiloxy)butane was 8.50 g of which 4.17 g was meso and 4.33 g was dl (dl : meso = 1.02). This was an 88% total yield.

The Attempted Pinacolic Reduction of Cyclohexanone by Chlorotrimethylsilane and Magnesium in Hexamethylphosphoramide

The same procedure was followed as for the reaction with acetophenone. However, the only compound that was isolated was starting material. The IR and NMR spectra and the VPC retention time were identical to those of the cyclohexanone used.

The Attempted Pinacolic Reduction of 2-Furyl Methyl Ketone by Chlorotrimethylsilane and Magnesium in Hexamethylphosphoramide

The same procedure was followed as for the reaction with acetophenone. However, only tars could be isolated as products.

PART II

ELUCIDATION OF THE STRUCTURE OF GOMATINE, A COMPOUND HAVING ANTIHISTAMINIC ACTIVITY, EXTRACTED FROM CROWN GALL TUMORS OF TOMATO PLANTS

INTRODUCTION

Antihistaminic Activity of Plant Gall Tumor Extracts

Galls are hypertrophies of plant tissues caused by insects, mites, bacteria, fungi, and possibly other organisms. These organisms may initiate either mechanical or chemical stimulii. The latter is probably the more important in the production of galls. Oak galls are examples of galls caused by wasps, whereas crown galls are induced by bacteria. Naturally occuring crown galls are found most frequently on the stems of tomato, tobacco, and sun flower. They are considered malignant tumors which produce metastases and frequently kill the host.

Feldberg and Kovacs[100] demonstrated that an ethanolic extract of oak gall tumors, when injected into guinea-pigs, protected the animals against a lethal dose of histamine aerosol and that the protection lasted for at least twenty-four hours, sometimes for as long as four days.

Broome et al[101] observed that an ethanolic extract of crown gall tumors of tomato plants, when injected into guinea-pigs, also protected the animals against a lethal histamine dose, sometimes for as long as forty-seven days.

Isolation of the Antihistaminic Principle(s) of Crown Gall Tumors

Kovacs et al[102,103] isolated a crude crystalline form of the antihistaminic principle(s) found in crown gall tumors of tomato plants. It closely resembled tomatine, a known constituent of tomato plants, having antihistaminic activity.[104] The crystalline crown gall substance resembled tomatine both in its physiological properties and in its chemical characteristics such as elemental composition (Table 8) and IR spectral data (Fig. 13).

TABLE 8

THE ELEMENTAL COMPOSITIONS OF THE CRYSTALLINE CROWN GALL SUBSTANCE, TOMATINE, AND GOMATINE

Element	% COMPOSITION		
Element	Crystalline crown gall substance	Tomatine*	Gomatine
Carbon	57.38	58.07	58.1
Hydrogen	7.91	8.09	8.4
Nitrogen	1.27	1.35	2**

Ref. 103

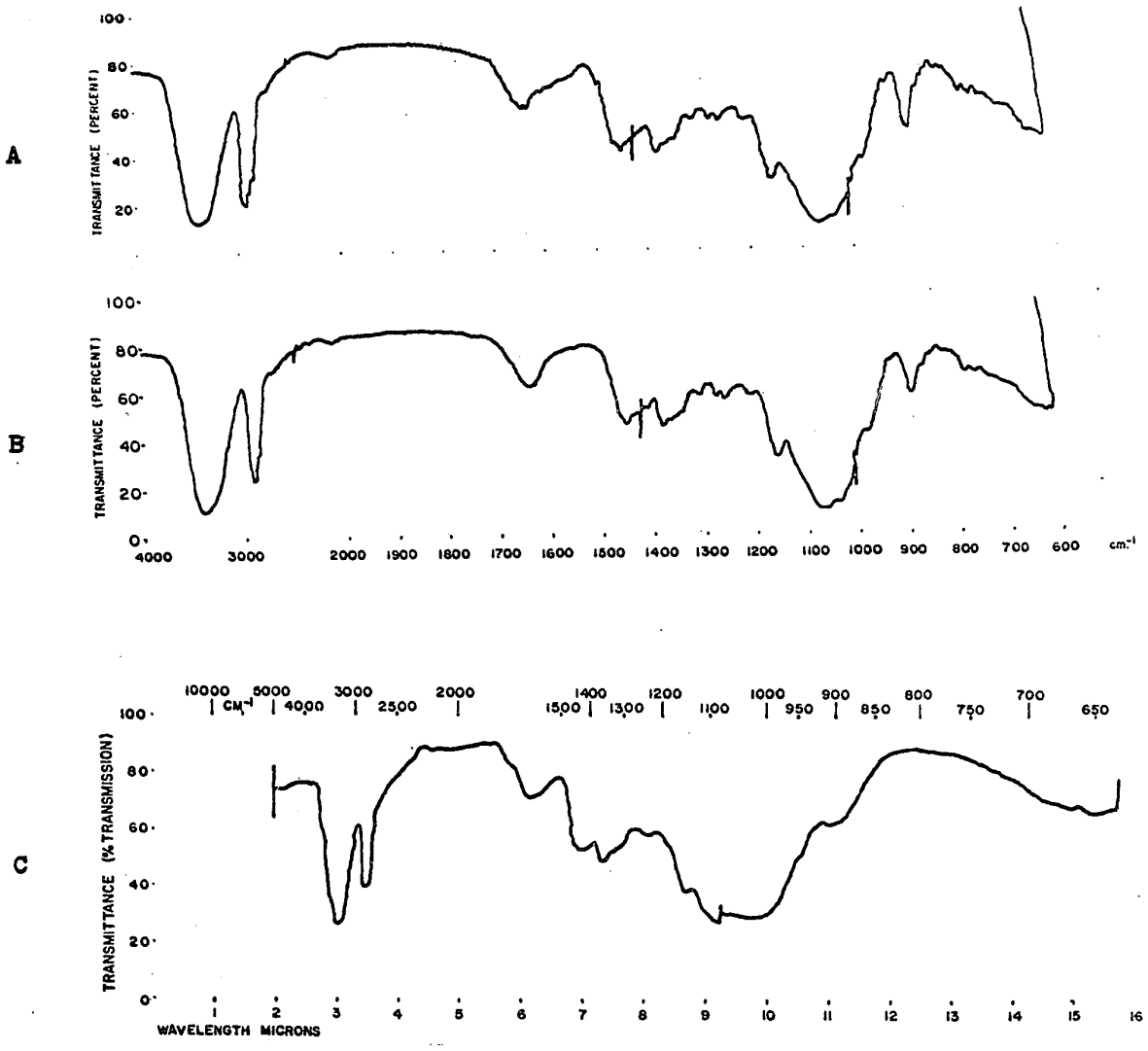
*Calculated values.

**Insufficient material was available for proper analysis.

Wakkary[103] separated tomatine out of this crude crown gall substance by precipitation with cholesterol. (Tomatine forms an ethanol insoluble complex with cholesterol). The crude tomatine-

Fig. 13

The IR Spectra of the Crystalline Crown Gall Substance (A), Tomatine (B), and Gomatine (C)



Ref. 103

free extract also exhibited antihistaminic activity. When it was analyzed by paper chromatography, there appeared eight spots, none of which had the same R_f value as tomatine. The crude tomatine-free extract was separated by gel filtration on a Sephadex LH-20 column and gave a crystalline material that showed antihistaminic activity. It was named "gomatine". Gomatine was similar to, but different from, tomatine. It came off close to tomatine on the Sephadex column, indicating that their molecular weights were similar. Their elemental compositions were quite similar (Table 8) as were their IR spectra (Fig. 13). However, their melting points were different: gomatine melted at 186-7°, whereas tomatine melted at 270°.[105]

Structure Elucidation of Tomatine

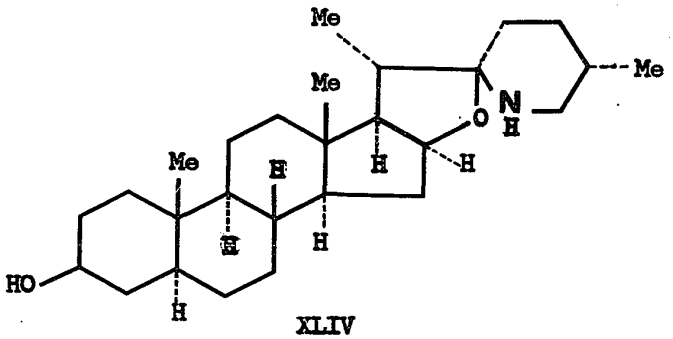
In 1950 Kuhn et al[106] and Ma and Fontaine[107] reported that the hydrolysis of tomatine yielded two moles of glucose, one mole of galactose, one mole of xylose, and the aglycone, tomatidine. The latter melted at 205-7° and on hydrogenation in 50% acetic acid with platinum oxide revealed the presence of a double bond.

In 1951 Fontaine et al[108] presented evidence that tomatidine was a steroidal secondary amine because, with digitonin it formed an alcohol-insoluble complex which is characteristic of a 3-(β)-ol sterol configuration, and by acetylation, tomatidine yielded an N,O-diacetyl derivative which indicated the presence of a secondary amino group. They also showed that the absorption of one mole of hydrogen by tomatidine, upon hydrogenation, was not due to a double bond as had been previously reported,[106] but may have been the result of the opening of an oxidic linkage, as was reported by Marker

et al[109] for sapogenins. Further evidence for the opening of an oxidic ring was that after hydrogenation an additional hydroxyl group appeared, since acetylation then added three instead of two acetyl groups.

The steroid structure of tomatidine was confirmed by Sato et al[110] who established that the point of attachment of the portion containing the secondary amine was at C-20.

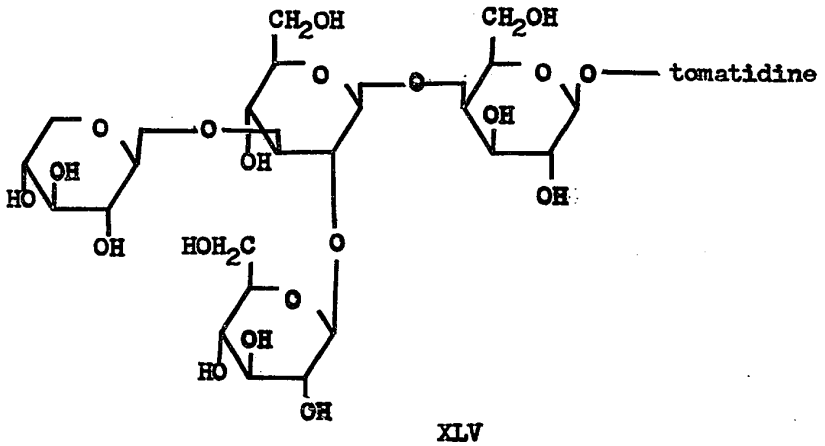
Thus, tomatidine is a 3-(β)-sterol having an oxidic linkage similar to the sapogenins and a secondary amino group. Therefore, the structure is similar to that of the sapogenins, except that a nitrogen atom is substituted for an oxygen atom in ring F. The absolute configuration of ring F was confirmed by Boll and Sjoberg.[111] Tomatidine has structure XLIV. A formal total synthesis of tomatidine has been published by Schreiber and Adam.[112]



XLIV

The tetrasaccharide moiety of tomatine, composed of one mole of D-xylose, two moles of D-glucose, and one mole of D-galactose, is called lycotetraose and is attached to the steroidal portion at the 3-hydroxy position. Kuhn et al[113] determined the structure of

lycotetraose by partial hydrolysis of tomatine in which D-xylose was lost, followed by methylation of the derived alkaloid and hydrolysis. Further partial hydrolysis and optical data confirmed that lycotetraose has structure XLV. (The point of attachment of tomatidine in the structure of tomatine is shown in structure XLV).



XLV

The object of the work to be described was to elucidate the structure of gomatine.

RESULTS AND DISCUSSION

Since gomatine was similar to tomatine as far as its probable molecular weight, elemental composition, and IR spectrum were concerned (see p. 93), it was assumed that its structure was also similar to that of tomatine. However, only ~20 mg of recrystallized gomatine were available for the structural determination, and so most chemical methods could not be used. The determination was done by VPC analysis, IR spectroscopy, and mass spectrometry.

Analysis of the Sugar Moiety of Gomatine

Gomatine was hydrolyzed with 5% hydrogen chloride in methanol and the sugars that were isolated were analyzed by VPC as their trimethylsilyl ethers according to the method used by Tschesche[114] for analyzing the sugars in tomatine.

It was found that three different samples of gomatine yielded the same sugars, and in the same ratio, as did tomatine (Fig. 14); namely two moles of glucose, one mole of galactose, and one mole of xylose.

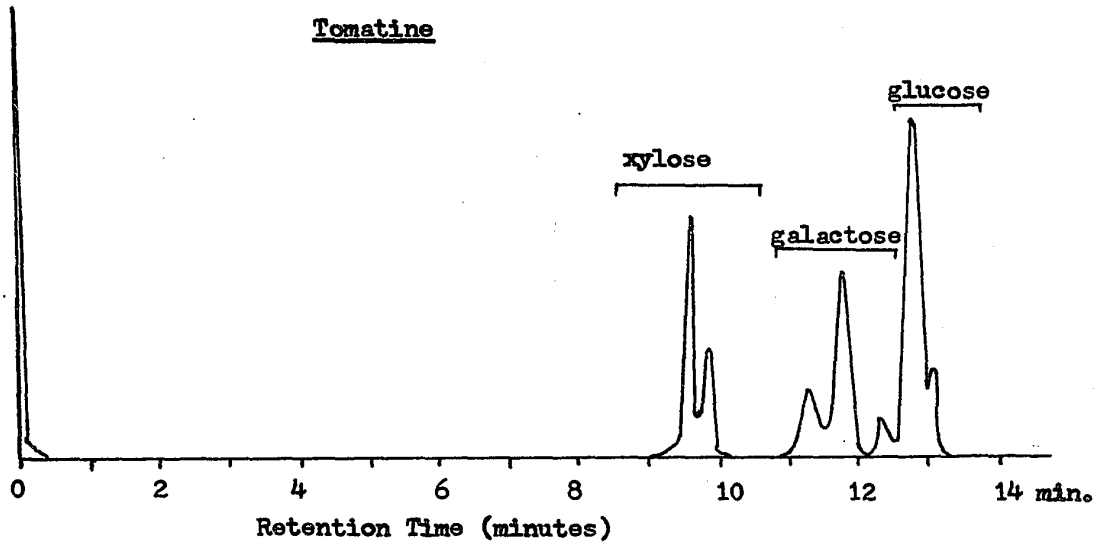
Structural Determination of the Steroidal Moiety of Gomatine

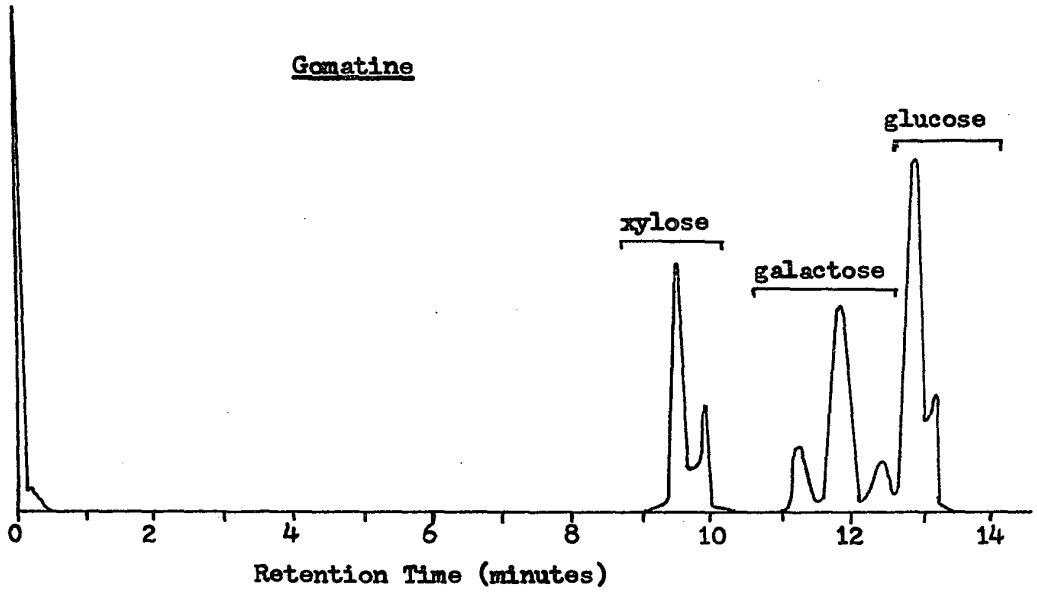
The steroidal aglycone that was left after gomatine was hydrolyzed was purified by preparative TLC and analyzed by mass spectrometry and IR spectroscopy.

The mass spectrum of tomatidine is shown in Fig. 15 and its accurate mass measurement is given in Table 9; those of a related compound, solasodine, are shown in Fig. 16 and Table 10 respectively. The most probable mass spectral fragmentation pattern for these two compounds, which gives rise to the observed ions, is shown in Fig. 17.

Fig. 14

Gas Chromatograms of the Trimethylsilyl Ethers of the Sugars Obtained From the Hydrolysis of Tomatine and Gomatine





Ratio of xylose:galactose:glucose = 1:1:2 for tomatine and gomatine.

Fig. 15

The Mass Spectrum of Tomatidine

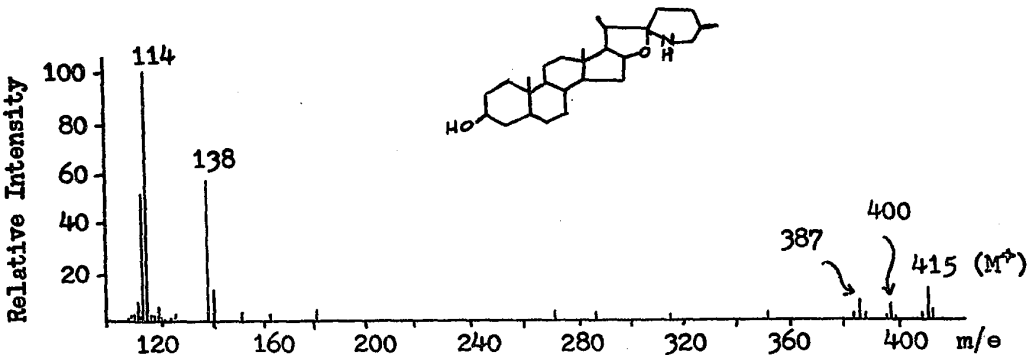


Fig. 16

The Mass Spectrum of Solasodine

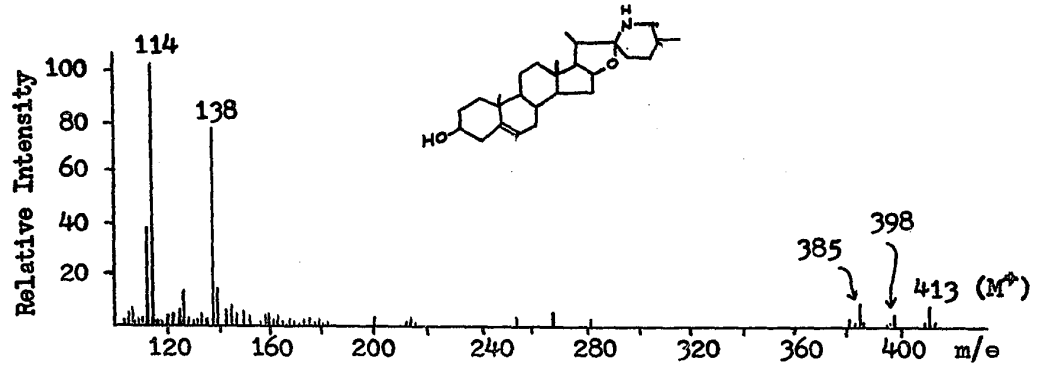


TABLE 9

ACCURATE MASS MEASUREMENT OF TOMATIDINE

Measured Mass	Calculated Mass	Elemental Composition
114.091509	114.091884	$C_6H_{12}NO$

continued

TABLE 9 (cont'd)

Measured Mass	Calculated Mass	Elemental Composition
138.128193	138.128268	$C_9H_{16}N$
387.349609	387.350097	$C_{26}H_{45}NO$
400.321691	400.321537	$C_{26}H_{42}NO_2$
415.345292	415.345011	$C_{27}H_{45}NO_2$

TABLE 10

ACCURATE MASS MEASUREMENT OF SOLASODINE

Measured Mass	Calculated Mass	Elemental Composition
114.091509	114.091884	$C_6H_{12}NO$
138.128193	138.128268	$C_9H_{16}N$
385.334358	385.334448	$C_{26}H_{43}NO$
398.305317	398.305888	$C_{26}H_{40}NO_2$
413.329506	413.329362	$C_{27}H_{43}NO_2$

Fig. 17

The Mass Spectral Fragmentation Pattern of

Tomatidine (T) and Solasodine (S)

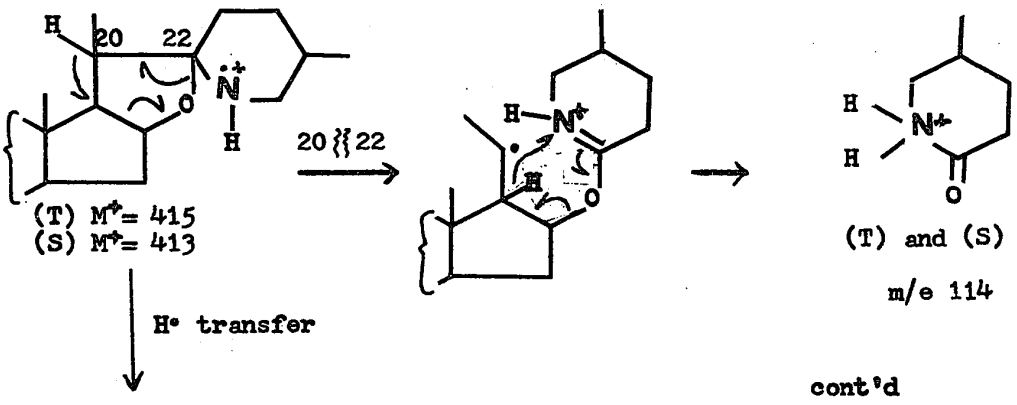


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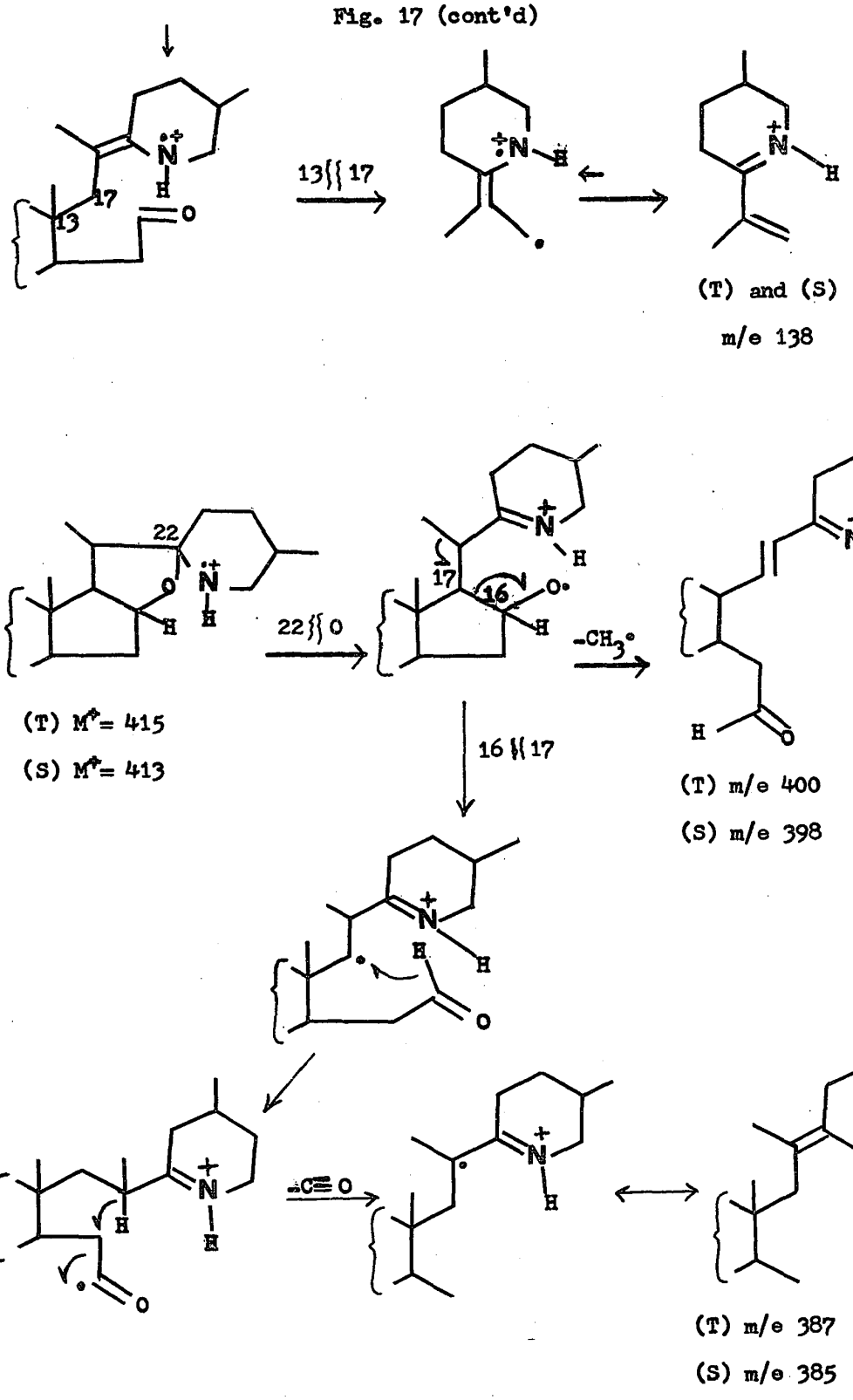
Fig. 17 (cont'd)


13 ⟦ 17
(T) and (S)
m/e 138
22 ⟦ O
(T) M⁺ = 415
(S) M⁺ = 413
-CH3°
16 ⟦ 17
(T) m/e 400
(S) m/e 398
-C≡O
(T) m/e 387
(S) m/e 385

The mass spectrum of "gomatidine", the steroidal moiety left when gomatine (sample I) was hydrolyzed, is shown in Fig. 18. and its accurate mass measurement is given in Table 11. The upper parts

Fig. 18

The Mass Spectrum of Gomatidine

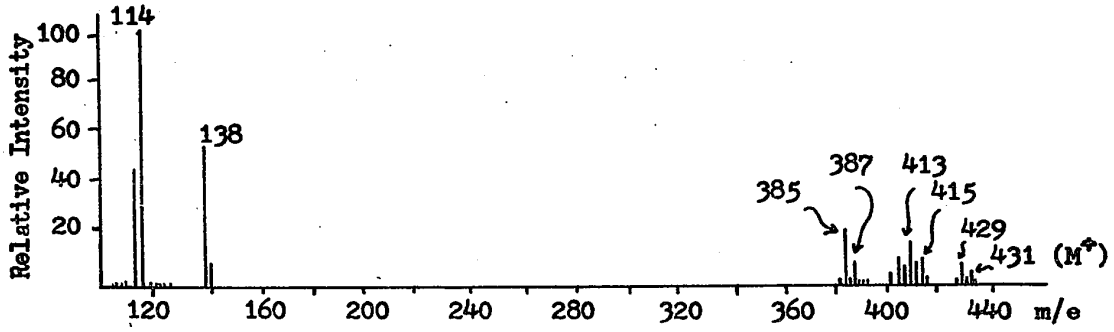


TABLE 11

ACCURATE MASS MEASUREMENT OF GOMATIDINE

Measured Mass	Calculated Mass	Elemental Composition
431.337 ± .004	431.339926	$C_{27}H_{45}NO_3$
429.322210	429.324246	$C_{27}H_{43}NO_3$
415.342119	415.345011	$C_{27}H_{45}NO_2$
413.332126	413.329362	$C_{27}H_{43}NO_2$
387.349609	387.350097	$C_{26}H_{45}NO$
385.333596	385.334448	$C_{26}H_{43}NO$
138.128171	138.128268	$C_9H_{16}N$
114.091207	114.091884	$C_6H_{12}NO$

of the mass spectra of two other samples of gomatidine, as well as sample I, are shown in Fig. 19. The largest peaks in all three samples were at m/e 114 and 138, as in Fig. 18 for sample I, and are not shown. Since these are the same as the largest peaks in the spectra of tomatidine and solasodine, and they are due to the same ions (accurate mass measurement), one may assume that gomatidine has the same type of structure as tomatidine as far as the D, E, and F rings are concerned. (Fig. 17 showed how these ions arise). The peaks at m/e 415, 400, and 387 in gomatidine sample II are much smaller relative to those at m/e 413, 398, and 385, respectively, than in sample I and they are negligible in sample III (Fig. 19); and the accurate mass measurement of these peaks (Table 11) indicated that they were the same as those of tomatidine. Therefore, these peaks probably represent the presence of contaminating tomatidine in gomatidine.

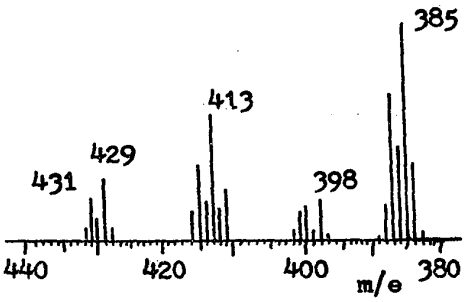
The accurate mass measurement of gomatidine (Table 11) showed that the molecular ion (m/e 431) had the composition of tomatidine with one more oxygen atom and that the peaks at m/e 413 and 385 had the same composition as those of solasodine. Thus, it was thought that gomatidine has the structure of tomatidine with an extra hydroxy group, and that the loss of water by the molecular ion in the mass spectral fragmentation led to an ion having a structure isomeric with solasodine and so gave the same mass spectrum. So both solasodine and gomatidine (sample I) were exchanged with methanol-d and their mass spectra were taken and compared to the unexchanged compounds (Fig. 20). For solasodine, there were a maximum of two exchangeable hydrogens (the peak at m/e 413 moved to 415 and 414, the

Fig. 19

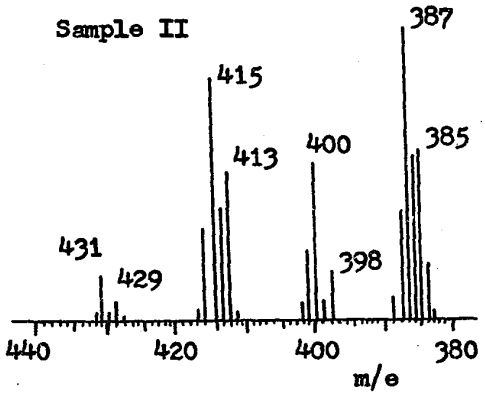
The Mass Spectra of Gomatidine and Gomatidine that was Reduced with Lithium Aluminum Hydride

Gomatidine

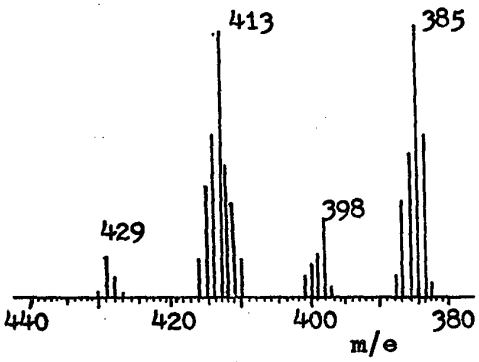
Sample I



Sample II

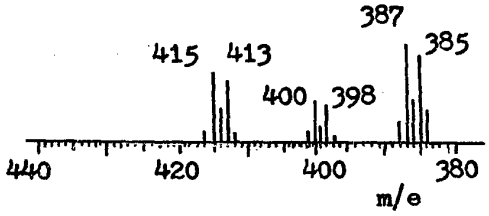


Sample III



Reduced Gomatidine

Samples I + II



Sample III

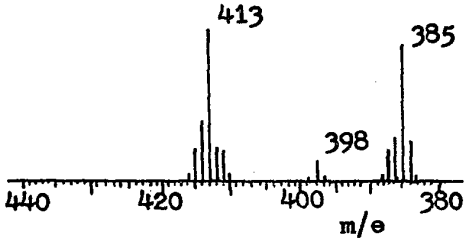
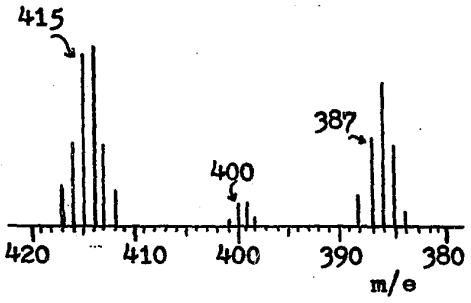


Fig. 20

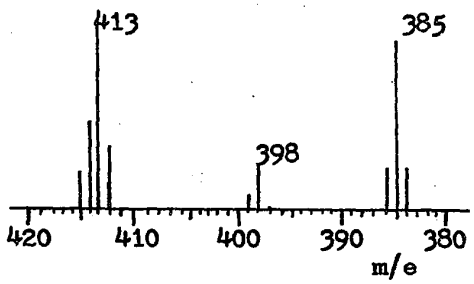
The Mass Spectra of Solasodine and Gomatidine Exchanged with Methanol-d Compared to those of Unexchanged Solasodine and Gomatidine

Solasodine

Exchanged

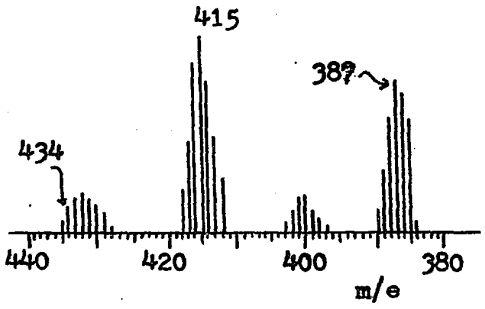


Unexchanged

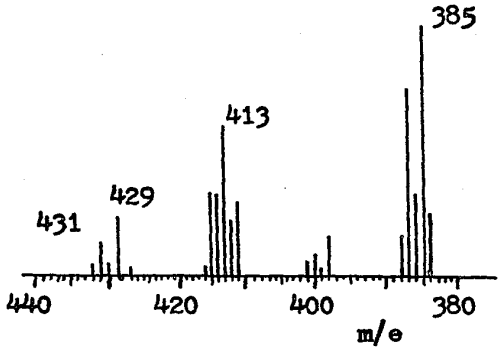


Gomatidine

Exchanged



Unexchanged



one at 398 to 400 and 399, and the one at 385 to 387 and 386 after exchange); whereas for gomatidine there were a maxmimum of three exchangeable hydrogens (the molecular ion moved as far as 434 from

431; the peaks at 413 and 385 showed only two exchangeable hydrogens since those peaks were due to the M^+-H_2O and $(M^+-H_2O)-CO$ ions, respectively). Thus, gomatidine seems to have the structure of tomatidine with an extra hydroxy group.

This type of structure can arise from the hydration of solasodine, if it was present, in the hydrolysis of gomatine. Therefore, a sample of solasodine was hydrolyzed under the same conditions that were used for gomatine and it was purified by preparative TLC in the same way as gomatidine was. The mass spectrum of the product so obtained was that of pure solasodine as in Fig. 16. Therefore, gomatidine is not just solasodine that was hydrated in the hydrolysis step.

The IR spectra of gomatidine (samples II and III) were identical. They were compared to the spectra of 7-α-hydroxy- and 9-α-hydroxytomatidine[115] (Fig. 21). The spectrum of gomatidine was similar to those of both of the above compounds; however, gomatidine had, in addition, a strong carbonyl stretching band at 1725 cm^{-1}. Thus, the peak at m/e 429 in the mass spectrum of gomatidine is probably due to a compound having the structure of tomatidine with a carbonyl group at some position.

Gomatidine (samples I and II were combined; and sample III) was then reduced with lithium aluminum hydride and the IR spectra were taken of the reduced products. The spectra were identical and one of them is shown in Fig. 21. The carbonyl group at 1725 cm^{-1}, that was in the spectrum of gomatidine, was almost gone, there were

Fig. 21

The IR Spectra of 7-α-hydroxytomatidine (A), 9-α-hydroxytomatidine (B), Gomatidine (C), Gomatidine that was Reduced with Lithium Aluminum Hydride (D), and Solasodine (E)

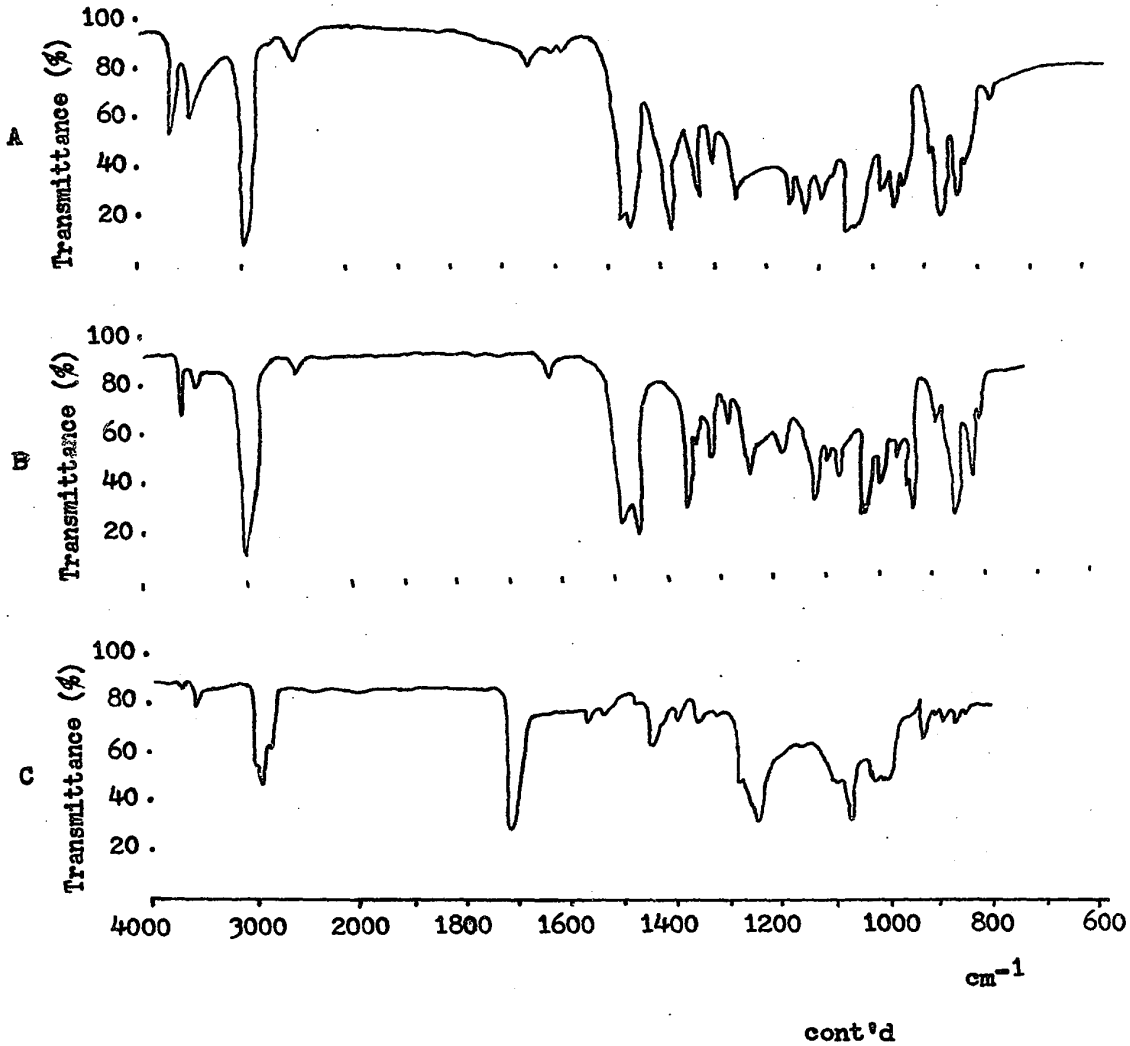


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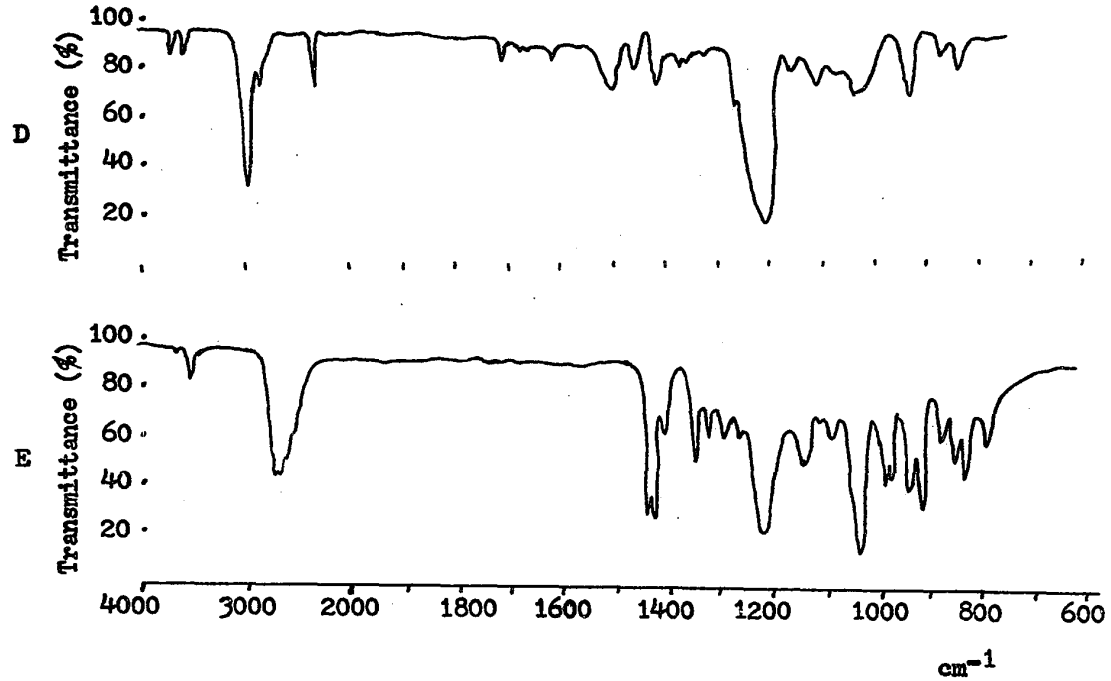
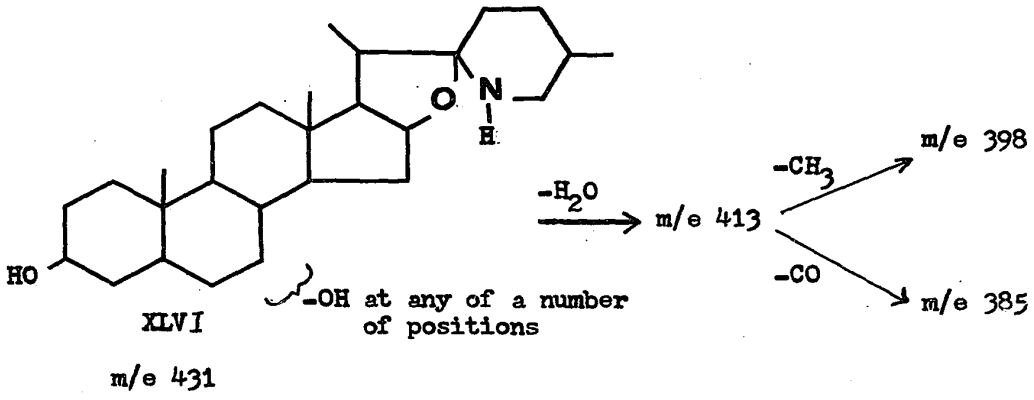
Fig. 21 (cont'd)



two hydroxy stretching frequencies (at 3690 and 3621 cm^{-1}) that were of equal intensity while in the spectrum of gomatidine the peak at 3605 cm^{-1} was much stronger then the one at 3675 cm^{-1}, and the C-O stretching band at 1200 cm^{-1} was much stronger than in the spectrum of gomatidine, indicating that there are probably more C-O groups in the reduced sample. However, the spectrum of reduced gomatidine did not match that of either 7-α-hydroxy- or 9-α-hydroxytomatidine[115], nor, for that matter, that of solasodine (Fig. 21). It may be a mixture of the first two compounds, or the hydroxy group may be in a different position altogether.

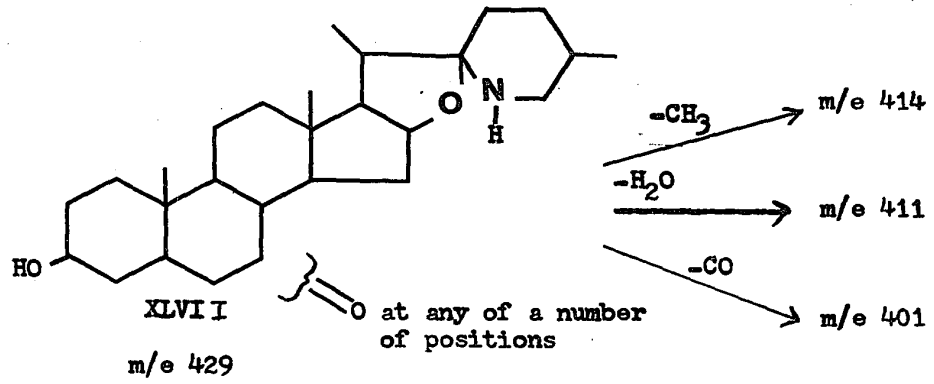
In the mass spectra of the samples of reduced gomatidine, the peak at m/e 429 disappeared, but so did the one at m/e 431 (Fig. 19), although the latter was expected to be present as the molecular ion. The peak at m/e 431 could also not be seen in the spectrum of sample III of unreduced gomatidine (Fig. 19). A likely explanation for this observation is that the molecular ion (m/e 431) loses water very readily to give the peak at m/e 413, and so the molecular ion itself is not seen in the mass spectrum.

Thus, it was concluded that gomatidine probably consists of the following species which give rise to the observed ions in the mass spectrum:



XLVI

m/e 431



XLVII

m/e 429

Both of the above species will give the major ions at m/e 114 and 138. Some samples of gomatidine were contaminated with tomatidine; thus, one cannot eliminate the possibility that the gomatidine could have been contaminated with solasodine as well since the mass spectra of gomatidine contained all of the peaks for solasodine (sample III showed only the peaks for solasodine; the molecular ion at m/e 431 was not seen). However, gomatidine sample III and the samples of reduced gomatidine were not just solasodine, since their IR spectra were different from that of solasodine.

The sugar moiety that was analyzed for gomatine may have been due to the contaminating tomatine in samples I and II. However, gomatine sample III, which was not contaminated with tomatine, also gave the same sugars and in the same ratio. The sugar moiety may be attached at the three hydroxy group of either or both of species XLVI and XLVII.

Summary

The antihistamine active compound isolated by Kovacs and Wakkary from crown gall tumors of tomato plants does not seem to be a pure compound, but a mixture of at least two compounds: one having the tomatine structure with an extra hydroxy group attached at one of several positions; and another having the structure of tomatine with a keto group at any of several positions. The antihistamine active compound was often contaminated with tomatine and it could possibly have been contaminated with a glycoalkaloid of solasodine as well.

EXPERIMENTAL

The Hydrolysis of Tomatine and Gomatine

The method of Tschesche[114] was followed. About 5-10 mg of tomatine or gomatine were hydrolyzed with 5 ml of a 5% solution of hydrogen chloride in methanol for five hours under reflux. After cooling, the solutions were diluted with twice the volume of water and the organic components were extracted three times with chloroform. The aqueous-methanolic layer was neutralized on an ion exchange column with rexyn 203 (OH) and the solvents were removed on the rotary evaporator at 65° by azeotroping with benzene. The sugars so obtained were dried overnight in a dessicator and silylated with bis(trimethylsilyl)acetamide.[116] The same procedure was carried out simultaneously on pure glucose, galactose, xylose, and a 1:1:1 molar mixture of these sugars for comparison purposes in the subsequent VPC analysis.

Silylation of Sugars with Bis(trimethylsilyl)acetamide[116]

The sugars were dissolved in 0.5 ml of pyridine and stirred under reflux with an excess of bis(trimethylsilyl)acetamide (0.5 ml) at 50° for 30 minutes. A calcium chloride drying tube was attached to the top of the condenser to keep the system dry.

Analysis of the Sugars Obtained from the Hydrolysis of Gomatine

The method of Tschesche[114] for the VPC analysis of the sugars from tomatine was followed. The silylated sugars were analyzed by

VPC on a silicone rubber column (UCW98), using a programmed temperature run from 150-225° at 10°/minute, with a post injection interval of two minutes. The helium flow rate was 35 ml/minute. Silylated glucose, galactose, xylose, and a 1:1:1 molar mixture of these sugars, all of which had been subjected to the same hydrolysis conditions as tomatine and gomatine, were analyzed as well as the silylated sugars obtained from the hydrolysis of tomatine and gomatine. It was seen that both gomatine and tomatine yielded, upon hydrolysis, two moles of glucose, one mole of galactose, and one mole of xylose (Fig. 14). Three different samples of gomatine were analyzed and the results were always the same. (See Table 12 for the quantities of gomatine used and of the sugars obtained).

Structure Elucidation of the Steroidal Moiety of Gomatine

The chloroform extracts from the hydrolysis of gomatine and tomatine were evaporated using a stream of dry nitrogen. The crude gomatidine and tomatidine so obtained were purified by preparative TLC using precoated sheets with fluorescent indicator added and a special developing apparatus designed for use with these sheets (all made by Kodak). The solvent system was benzene-methanol 9:1. The bands were visualized by UV light and those having an R_f value close to that of tomatidine were extracted with 13% methanol in chloroform. Pure tomatidine had an R_f value of 0.40 in this system. Three different samples of gomatidine were obtained. (See Table 12 for quantities of gomatine used and of gomatidine isolated).

The mass spectra were taken of the tomatidine so obtained (same as that of pure tomatidine, Fig. 15) and of the three samples of gomatidine (Figs. 18 and 19). The IR spectra ($CHCl_3$) were taken of samples II and III of gomatidine on a Perkin-Elmer 521 spectrophotometer. They were identical (Fig. 21).

TABLE 12

YIELDS OF SUGARS AND GOMATIDINE FROM THE HYDROLYSIS OF GOMATINE

Sample Number	Gomatine (mg)	Sugars (mg)	Crude Gomatidine (mg)	Pure Gomatidine (mg)	Isolated at R_f
I	6.3	3.5	3.7	2.6	0.39
II	5.6	3.1	4.6	1.0	0.42
III	43.5*	8.0	35.1	7.4	0.35

*This sample of gomatine was very crude.

The Reduction of Gomatidine with Lithium Aluminum Hydride

Gomatidine samples I and II were combined and reduced and gomatidine sample III was reduced by the method of Micovic and Mihailovic.[117] A flask equipped with a reflux condenser, magnetic stirring bar, and a dropping funnel, and protected from atmospheric moisture by drying tubes was charged with a large excess of lithium aluminum hydride (~ 3 mg; 0.1 mmoles) and anhydrous ether (3 ml). A solution of gomatidine (samples I and II, 3.6 mg = 0.005 mmoles;

sample III, 7.4 mg = 0.01 mmoles) in anhydrous ether (1 ml) was added at a rate which maintained gentle refluxing for about 1½ minutes. Refluxing was continued for 30 minutes, the mixture was cooled, and 2 ml of water were added continuously by drops (no foaming). The solution was then added to cold dilute sulphuric acid to decompose the complex aluminum compounds and to dissolve the precipitated aluminum hydroxide. The ether was removed, the aqueous solution was basified to release the steroid (a secondary amine), and extracted with chloroform. Removal of the solvent left the reduced gomatidine (samples I and II, 2.2 mg; sample III, 5.0 mg) whose mass spectra were taken (Fig. 19). Their IR spectra ($CHCl_3$), taken on a Perkin-Elmer 521 spectrophotometer, were identical (Fig. 21).

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