hot water caused decomposition. The corresponding chloride (R = $COCH_2NC_5H_5^+Cl^-$) was very soluble in cold water. Preparing it in relatively good yield was difficult because its rate of formation was lower, as expected, than that of the iodide and because part of the product was decomposed as the reaction proceeded, apparently by transesterification with ethanol employed as a solvent.[7] The chloride was hydrolyzed in aqueous solution to N-carboxymethylpyridinium chloride (presumably) and what appeared to be a mixture of epipodophyllotoxin[3] and podophyllotoxin. In the presence of a buffer (*p*H 7), podophyllotoxin free of its epimer was isolated.[8]

Experimental[9,10]

Podophyllotoxin Chloroacetate (I, R = $COCH_2Cl$).—To an ice-cooled solution of 9.6 g. of anhydrous podophyllotoxin[3a] (I, R = H) in 30 ml. of dry pyridine was added with swirling 9 ml. of chloroacetic anhydride. The mixture was kept at room temperature for 15 minutes, then poured with stirring into 500 ml. of ice and water. The yellow solid was collected after an hour, washed thoroughly with water and dissolved in chloroform. The solution was washed with water, dried over magnesium sulfate, concentrated and chromatographed on alumina. Elution with chloroform and concentration with addition of ethanol yielded 8.95 g. (79%) of colorless needles, m.p. 207–207.5° (immersed at 195°). Recrystallization from chloroform–ethanol provided material, m.p. 208–209° (immersed at 150°), 209–210° (immersed at 195°), $[\alpha]^{22}D$ −140° (*c* 1.05, chloroform).

Anal. Calcd. for $C_{24}H_{23}O_9Cl$: C, 58.72; H, 4.72; Cl, 7.22. Found: C, 58.64; H, 4.86; Cl, 7.22.

Podophyllotoxin Bromoacetate (I, R = $COCH_2Br$).—An ice-cooled mixture of 1.3 ml. of bromoacetyl bromide and 5 ml. of chloroform was treated with 1.4 ml. of dry pyridine, then with 2.07 g. of I (R = H) in 5 ml. of chloroform. The dark brown solution, after 10 minutes at room temperature, was poured into 100 ml. of ice-water. The combined chloroform solutions, obtained by separating layers and extracting the aqueous phase with additional solvent, were washed with 0.2 *N* hydrochloric acid, sodium bicarbonate solution and water, then dried, concentrated and chromatographed. Concentration with addition of ethanol gave 0.91 g. (34%) of colorless needles, m.p. 192° (immersed at 150°), $[\alpha]^{22}D$ −133° (*c* 1.03, chloroform).

Anal. Calcd. for $C_{24}H_{23}O_9Br$: C, 53.84; H, 4.35; Br, 14.93. Found: C, 53.79; H, 4.63; Br, 14.82.

Podophyllotoxin Iodoacetate (I, R = $COCH_2I$).—A solution of 7.36 g. of the chloroacetate I (R = $COCH_2Cl$) in 75 ml. of acetone was refluxed with 25 g. of sodium iodide for four hours, then poured into a stirred mixture of 600 ml. of water and 75 ml. of chloroform. The aqueous layer was extracted with additional chloroform and the combined chloroform solutions washed with very dilute aqueous sulfur dioxide, then with water and dried. Concentrating and adding an equal volume of hexane yielded 8.23 g. (94%) of colorless needles, melting at 190° with effervescence, darkening and liberation of iodine (immersed at 150°); m.p. 192° (dec.) after recrystallization from chloroform–hexane; $[\alpha]^{22}D$ −128° (*c* 1.01, chloroform).

Anal. Calcd. for $C_{24}H_{23}O_9I$: C, 49.50; H, 3.98; I, 21.79. Found: C, 49.32; H, 3.90; I, 21.72.

Picropodophyllin Chloroacetate (I, R = $COCH_2Cl$).—The compound was obtained in 74% yield from picropodophyllin[3a] (I, R = H) by the procedure used for the epimeric[3] podophyllotoxin chloroacetate. It formed colorless cottony needles, which melted at 154–155° (immersed at room temperature), resolidified at 156° and remelted at 178–191°; $[\alpha]^{21}D$ +47° (*c* 1.01, chloroform).

Anal. Calcd. for $C_{24}H_{23}O_9Cl$: C, 58.72; H, 4.72; Cl, 7.22. Found: C, 58.76; H, 4.72; Cl, 7.36.

Acetylpodophyllotoxin-ω-pyridinium Chloride (I, R = $COCH_2NC_5H_5^+Cl^-$).—A solution of 10 g. of the chloroacetate I (R = $COCH_2Cl$) in 50 ml. of chloroform and 50 ml. of ethanol was refluxed with 2.5 ml. of dry pyridine with exclusion of moisture for seven hours, then evaporated under reduced pressure. The solid was dissolved in 50 ml. of hot chloroform. Adding 75 ml. of hot ethyl acetate precipitated pale crystalline material, which was collected after standing at room temperature; yield 2.56 g. (21.4%), m.p. 153–154° (effervescence and darkening, immersed at room temperature). Recrystallization from methanol–ethyl acetate provided leaflets, m.p. 158–159° (dec.), $[\alpha]^{20}D$ −102° (*c* 0.57, water), $[\alpha]^{21}D$ −97° (*c* 0.54, methanol). The product was faintly greenish when still moist with solvent, but took on a brilliant pink color upon drying in air. It then contained one mole of water of crystallization, which could not be removed completely without partial decomposition. The compound was very soluble in water and methanol, less soluble in chloroform and nearly insoluble in ethyl acetate.

Anal. Calcd. for $C_{29}H_{28}O_9NCl \cdot H_2O$: C, 59.23; H, 5.14; N, 2.38; Cl, 6.03; H_2O, 3.06. Found: C, 58.99; H, 5.30; N, 2.56; Cl, 6.03; wt. loss (vac., 100°), 2.89.

A solution of 588 mg. of the compound in 30 ml. of 0.2 *M* sodium phosphate buffer (*p*H 7.3) became milky within five minutes, while prismatic needles began to separate after 10 minutes. The mixture was kept at 37° for 64 hours and filtered. The *p*H of the filtrate was 7.05; the solid (330 mg., 80%) melted at 183–185° (after drying at 110° *in vacuo*)[3a] and gave the infrared spectrum of podophyllotoxin. When 500 mg. of the pyridinium chloride in 10 ml. of water was kept at 60° for 17 hours, a plastic mass separated, which crystallized gradually; yield 327 mg. (93%), m.p. 139–141° (dec.). The infrared spectrum appeared to indicate that the product was a mixture of epipodophyllotoxin[3] with a lesser amount of podophyllotoxin. The filtrate was acid to congo red.

Acetylpodophyllotoxin-ω-pyridinium Iodide (I, R = $COCH_2NC_5H_5^+I^-$).—A solution of 1.16 g. of the iodoacetate I (R = $COCH_2I$) in 5 ml. of chloroform, 5 ml. of ethanol and 0.24 ml. of pyridine was refluxed for 30 minutes, at which time a yellow solid separated. This was removed and the mother liquor concentrated with addition of chloroform to obtain further solid. The combined crops (1.06 g., 78%) were washed with chloroform; m.p. 155–156° (foaming, immersed at room temperature). The product was purified by dissolving it in methanol, concentrating and adding chloroform. It then formed faintly yellowish needles, m.p. 156–157° (dec.), much less soluble in water, methanol and chloroform than the corresponding chloride.

Anal. Calcd. for $C_{29}H_{28}O_9NI \cdot H_2O$: C, 51.26; H, 4.45; I, 18.68. Found: C, 51.39; H, 4.43; I, 18.41.

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[7] The product could not be obtained in the absence of ethanol; this is in line with the experience that polar solvents strongly accelerate the rate of analogous quaternizations; *cf.* E. D. Hughes, *Trans. Faraday Soc.*, **37**, 603 (1941).

[8] V. S. Waravdekar, A. D. Paradis and J. Leiter, *J. Natl. Cancer Inst.*, **14**, 585 (1953), ascribe the tumor-damaging action of the quaternary chloride to the liberation of podophyllotoxin *in vivo*.

[9] Melting points varied with the temperature of immersion and rate of heating. The values reported are corrected and were obtained with the Hershberg apparatus by heating rapidly to within 5° of the melting point, then raising the temperature gradually at the rate of 2°/min.

[10] We are indebted to Dr. W. C. Alford and co-workers for the microanalyses.

Synthesis of Monochloroacetone

BY ROBERT E. VAN ATTA, HARRY D. ZOOK AND PHILIP J. ELVING

RECEIVED AUGUST 31, 1953

In the course of an investigation of halogenated ketones, monochloroacetone uncontaminated by *sym*- or *unsym*-dichloroacetone was required. Owing to the very slight difference in boiling points of chloroacetone and *unsym*-dichloroacetone,[1] it is practically impossible to separate them completely

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[1] E. R. Buchman and H. Sargent, THIS JOURNAL, **67**, 401 (1945).

by fractionation. Therefore, a method of preparation was sought which would produce chloroacetone with little possibility of forming polychloro compounds; a synthesis from acetyl chloride and diazomethane was found to fulfil this requirement. This type of synthesis has been applied previously to the synthesis of several higher-molecular weight chloroalkyl and chloroaryl ketones.[2] The intermediate diazoacetone was converted directly by dry hydrogen chloride to monochloroacetone in 68% over-all yield. The product boiled at 118–119° at 736 mm. and analyzed correctly for the monochloro compound.

Experimental.—A dried ether solution (approximately 500 ml.) containing 0.5 mole of diazomethane was placed in a 1000-ml. three-necked flask and Eastman Kodak practical grade acetyl chloride (0.25 mole) was added slowly from a dropping funnel with constant stirring of the solution which was maintained at a temperature not greater than 5°. The reaction mixture was allowed to stand for two hours after the addition of the acetyl chloride and was then saturated with dry hydrogen chloride over a period of two hours. The bulk of the ether was removed by distillation and the residual solution fractionated through a small column. The product boiling at 118–119° at 736 mm., d^{25}_4 1.1260, weighed 15.8 g. (68% based on acetyl chloride). The reported constants for monochloroacetone[1] are: b.p. 118–120° at 760 mm. and d^{25}_4 1.123.

Anal. Calcd. for C_3H_5OCl: Cl, 38.3. Found: Cl (Stepanov), 38.4.

Acknowledgment.—The authors wish to thank the Atomic Energy Commission which supported the work described.

[2] D. A. Clibbens and M. Nierenstein, *J. Chem. Soc.*, **107**, 1491 (1915); W. Bradley and R. Robinson, *ibid.*, 1310 (1928); W. Bradley and G. Schwarzenbach, *ibid.*, 2904 (1928); W. D. McPhee and E. Klingsberg, *Org. Syntheses*, **26**, 13 (1946); J. R. Catch, D. F. Elliott, D. H. Hey and E. R. H. Jones, *J. Chem. Soc.*, 278 (1948).

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Intramolecular Rearrangement of Isopropenyltrimethylsilane[1]

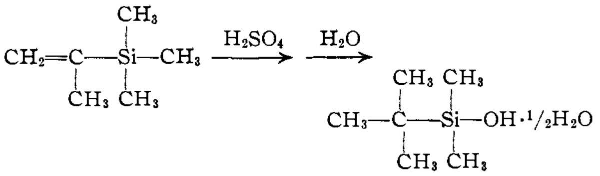
BY LEO H. SOMMER AND F. JAMES EVANS

RECEIVED JULY 29, 1953

Previous studies have demonstrated the phenomenon of intramolecular rearrangement of alkyl from silicon to carbon in chloromethyltrimethylsilane,[2] α-chloroethyltrimethylsilane, α-chloroethyltriethylsilane and dichloromethyltrimethylsilane.[3] While these rearrangements are of interest from the standpoint of demonstrating that the Wagner–Meerwein change is sufficiently general so as to include organosilicon rearrangements, a number of problems related to these new rearrangements are unsolved.

For example, in all four of the rearrangements thus far reported the reagent used was aluminum chloride and the starting material comprised an α-chloroalkylsilane.

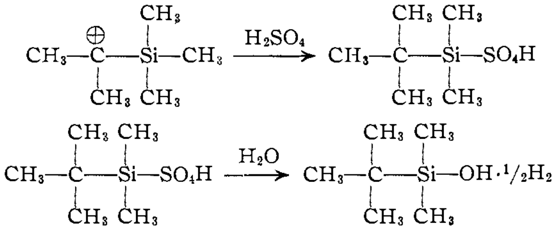
In the present work we have found that addition of isopropenyltrimethylsilane to concentrated sulfuric acid followed by treatment of the resulting solution with water gives *t*-butyldimethylsilanol hemihydrate.



$$CH_2{=}C(CH_3)-Si(CH_3)_2-CH_3 \xrightarrow{H_2SO_4} \xrightarrow{H_2O} CH_3-C(CH_3)_2-Si(CH_3)_2-OH\cdot{}^1/_2H_2O$$

Conversion of the hydrate to the pure silanol and comparison with an authentic sample of silanol synthesized by an unequivocal method[4] showed the substances to be identical.

The above reaction clearly involves rearrangement of methyl from silicon to carbon, and probably proceeds through an α-carbonium ion intermediate.[2,3]



$$CH_3-\overset{\oplus}{C}(CH_3)-Si(CH_3)_2-CH_3 \xrightarrow{H_2SO_4} CH_3-C(CH_3)_2-Si(CH_3)_2-SO_4H$$

$$CH_3-C(CH_3)_2-Si(CH_3)_2-SO_4H \xrightarrow{H_2O} CH_3-C(CH_3)_2-Si(CH_3)_2-OH\cdot{}^1/_2H_2O$$

Experimental

Synthesis of Isopropenyltrimethylsilane.—Addition of 10 moles of isopropylmagnesium chloride in 3 liters of ether to 22 moles of silicon tetrachloride dissolved in 550 ml. of dry ether over a period of 2 hours with stirring and cooling was followed by heating of the reactants on the steam-bath at reflux temperature for 12 hours. After removal of the ether and excess silicon tetrachloride by distillation, the product was rapidly distilled under vacuum to effect removal from the magnesium salts. Fractional distillation of the crude product so obtained gave isopropyltrichlorosilane, b.p. 119° at 736 mm., 812 g., a yield of 46%.

Anal. Calcd. for $C_3H_7SiCl_3$: Si, 15.99; Cl, 60.1. Found: Si, 16.05; Cl, 59.8.

Chlorination of isopropyltrichlorosilane (10.2 moles) with sulfuryl chloride (8.2 moles) in the presence of 1 g. of benzoyl peroxide by the method of Kharasch[5] gave, after fractional distillation of the product, α-chloro-*i*-propyltrichlorosilane (0.775 mole), b.p. 151°, and β-chloro-*i*-propyltrichlorosilane (2.62 moles), b.p. 164°.

The α-chloro-*i*-propyltrichlorosilane so obtained is a white, waxy solid which becomes granular on standing and sublimes readily at room temperature giving fern-like crystals. The melting point of the crystals determined in a sealed tube was found to be 109–110°.

Anal. Calcd. for $C_3H_6SiCl_4$: Si, 13.2; Cl (attached only to silicon), 50.2. Found: Si, 13.2; Cl (by alkali titration), 50.4.

The β-chloro-*i*-propyltrichlorosilane is a water-white liquid. Titration with standard sodium hydroxide of a methanol solution of this substance gave, as expected for a β-chloroalkylsilane,[6] complete reaction of the beta C–Cl bond as well as of the chlorine attached to silicon.

Anal. Calcd. for $C_3H_6SiCl_4$: Si, 13.2; Cl, 66.9. Found: Si, 13.0; Cl, 66.6.

Dehydrochlorination of β-chloro-*i*-propyltrichlorosilane with quinoline[7] gave in 76% yield isopropenyltrichlorosilane, b.p. 113° at 736 mm.

Anal. Calcd. for $C_3H_5SiCl_3$: Cl, 60.7. Found: Cl, 60.7.

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[1] Paper 39 in a series on organosilicon chemistry. For Paper 38 see THIS JOURNAL, **76**, 1030 (1954).

[2] F. C. Whitmore, L. H. Sommer and J. Gold, THIS JOURNAL, **69**, 1976 (1947).

[3] L. H. Sommer, D. L. Bailey, J. R. Gould and F. C. Whitmore, *ibid.*, **75**, 801 (1953).

[4] L. H. Sommer and L. J. Tyler, *ibid.*, **76**, 1030 (1954).

[5] M. S. Kharasch and H. C. Brown, *ibid.*, **61**, 2142 (1939); L. H. Sommer and F. C. Whitmore, *ibid.*, **68**, 485 (1946).

[6] L. H. Sommer, G. M. Goldberg, E. Dorfman and F. C. Whitmore, *ibid.*, **68**, 1083 (1946).

[7] D. T. Hurd, *ibid.*, **67**, 1813 (1945).