Silicon Derivatives of Medicinal Agents: Derivatives of P-Aminosalicylic, Salicylic and Benzoic Acids

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SUMMARY

Synthesis and characterisation of organosilicon derivatives of P-Aminosalicylic, Salicylic and benzoic acids are described. P-Amino Salicylic, Salicylic and benzoic acids are medicinal compounds which have been used as antitubercular, antibacterial, antifungal, Keratolytic (dermatophytoses) agents and also as preservatives. Silylation of these compounds with organosilicon reagents in acetone, tetraethoxy-silane, toluene and benzene have been prepared. These new silicon derivatives of benzoic, salicylic and P-aminosalicylic acids were obtained (i) by refluxing P.A.S. with silicon tetrachloride in tetraethoxy-silane in a molar ratio (4:1) to give compound (1) as hydrochloride. Similar compound was obtained in good yield when the same reaction (i) was carried out in acetone by stirring at 25°C) The reaction of P.A.S. with tetraethoxy-silane in molar ratios (1:2) or (1:4) carried out in benzene or tetrahydrofuran (ii) gives an unexpected interesting identical complex compound (ii) with a high quantitative yields in each of the two solvents.

Tetraethoxy silane is the reaction medium of salicylic acid with silicon tetrachloride in an equimolar ratio (1:1) to give compound (iii). This reaction presumbaly undergoes two stage reactions. The first state reaction presumably gives benzo-2,2-dichloro-2-sila-1, 3-dioxan-4-one which later reacted with tetraethoxy-silane to give benzo-2,2-diethoxy-2-sila-1,3-dioxan-4-one(iii).

The ethoxysilyl derivatives of salicylic and benzoic acids (iv) were synthesized by refluxing the acids with an excess of tetraethoxy-silane in benzene or toluene and the fractional distilation of ethanol formed as an azeotrope with benzene or toluene.

$$n\text{AroH} + \text{Si}(\text{OC}_2\text{H}_5)_4 \rightarrow (\text{Aro})n\text{Si}(\text{oC}_2\text{H}_5)_{4-n} + n\text{C}_2\text{H}_5\text{OH})$$

The identities of these compounds have been established by their elemental anlyses, infra-red spectra, melting points and Mass spectral analyses.

The derivatives are of interest, since silylation of medicinal agents has been known to alter their physico-chemical properties and Pharmacokinetics[1]. The purpose of this work was not only to establish conditions at which the silyl derivatives of these medicinal active acids could be synthesized but also to examine their biological activities and their release rates from an oitment base which are going to be reported later.

However, since P.A.S. is one of the antitubercular agents, the presence of silicon in the P.A.S.-silicon complex may presumably further prolong and increase the antitubercular activity of P.A.S. in the body. Reports showed that silicon is present in nearly all the body tissues and its compounds are less toxic when applied orally. The activity of each of the antitubercular compounds is suppressed or inhibited by the addition of certain metal ions e.g. Cu^{2+}, Co^{2+}, Ni^{2+}, Ca^{2+} and mg^{2+} has been reported.[2,3] Of these metals or metal ions, silicon does not possess such an inhibitory effect.

Since Phenyl-P-amino salicylate is an oily ester and was reported to have been administered orally as antitubercular agent,4,5 P.A.S.-silicon adduct could also applied in analogous manner.

EXPERIMENTAL

Reagents and analytical techniques

P–amino salicylic acid was of British Pharmaceutical Codex purity and supplied by British Drug Houses Limited. Salicylic and benzoic acids were analar grades obtained from May and Baker Chemical Laboratories. These acids were dried in vacuo over potassium hydroxide prior to use. Tetraethoxy silane was analar grade obtained from Hopkin and Williams and was used as supplied. Benzene, tetrahydrofuran, toluene, and acetone were laboratory reagent grades which were dried over molecular sieve type (4A) before use. Reactions were carried out in a 250cm^3 three-neck round bottom flask equipped with a reflux condenser, dropping funnel, thermometer and a mechanical stirrer.

Carbon, hydrogen and nitrogen were estimated by the Chemistry department analyst of University of Ife, Ile-Ife. Oxygen was estimated by difference.

The infra-red spectra were recorded in the region 400-4000cm^{-1} with a UNICAM grating spectrophotometer (model S.P. 110) using KBr plates.

Silicon content was estimated gravimetrically as silicon dioxide by the method described by Vogel.[6] Mass spectra were recorded using an A.E.I. Model M.S 12 Mass Spectrometer with gas chromatograph. Since these compounds are not fully soluble in all the organic solvents, the n.m.r. analysis are not carried out.

PROCEDURE

(i) Reaction of Silicon tetrachloride with P-amino Salicylic acid in tetraethoxy-silane.

To a stirred solution of P-aminosalicylic acid (7.657g, 0.05mol.) in tetraethoxy-silane (110ml) was added slowly from a dropping funnel silicon tetrachloride (2.125g, 0.0125mol) in tetraethoxy silane (30ml.) at 25°C under argon. The reaction flask was

heated at constant temperature of 90°C for 7 hours. After this period the white precipitates produced was filtered off and thoroughly washed with acetone and dried in vacuo yield 9.12g (58.31%), m.p. 224-227°C (Decomp).

Found: C,42.63%; H,3.62%, N,6.98%, Si,3.60%, $C_{28}H_{28}N_4O_{12}Cl_4Si$ requires C,42.97%; H,3.58%; N,7.16%; 0,24.55%; Cl,18.16%; Si,3.58%.

Molecular ion at m/e 783. The crystalline compound is slightly soluble in polar organic solvents, insoluble in non-polar solvents but soluble in aqueous acidified solutions:

Reaction of silicontetrachloride with P-aminosalicylic acid in acetone.

To a stirred solution of P-aminosalicyclic acid (7.655g, 0.05mol.) in acetone (150ml) was added slowly from a dropping funnel silicon tetrachloride (2.124g, 0.0125mol.) in acetone (50ml.) under argon at 25°C On addition of silicon tetrachloride in acetone, a white solid was precipitated out and stirring continued for another 2 hours. The white precipitates were filtered off in a sintered glass funnel, washed several times with acetone and finally dried in vacuo over KOH. The yield was 9.5g, (60.74%), m.p. 227-230°C (Decomp).

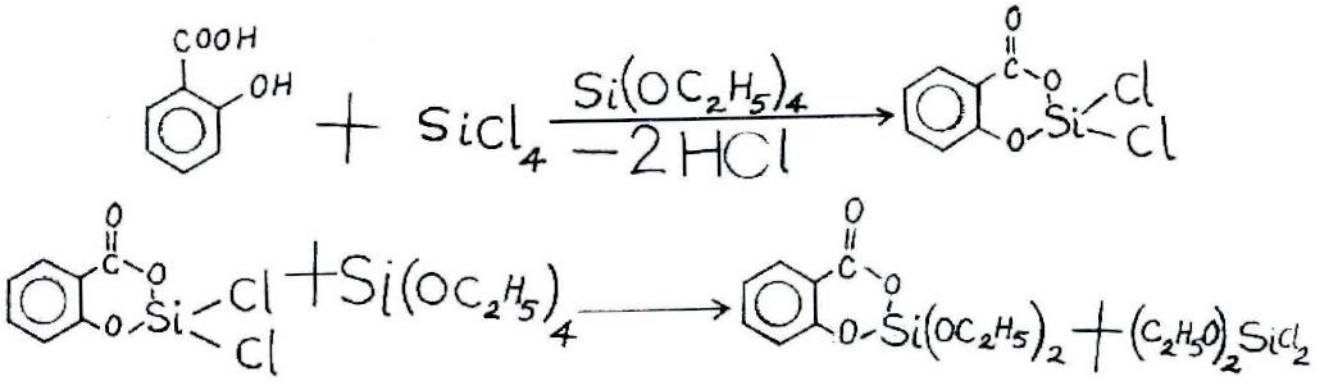
Found: C,42.77%; H,3.60%; N,7.09%; Si,3.54%. $C_{28}H_{28}N_4O_{12}Cl_4Si$ requires C,42.97%; H,3.58%; N,7.16%; 0,24.55%; Cl,18.16%; Si,3.58%.

Molecular ion m/e 782. The physical properties of this compound was similar with that of the solid obtained from the reaction of P.A.S. with SiCl4 in tetraethoxy-silane described above.

The infrared spectra of the two solids in nujolmull are identicals which showed very strong and large characteristics NH^+_3 absorption bands between 2800[3] 3000cm^{-1} Other strong NH^+_3 absorptions shown in the spectrum are at 1590 and 1510cm-1 respectively. The other bands are:- the strong νC-O and OH band at 1200cm^{-1}; strong νC=O band at 1695cm-1. very strong νC-O absorption at 1250cm-1, followed by the ν_{as} and ν_{sym}. absorptions of SiO4 at 809 and 787 cm-1 respectively. Observation showed that the missing absorption bands at 1448, 766 and 1215cm-1 presumably belong to δOH of Carboxylic acid, ν_sSiNSi and δSiNH.

(ii) Reaction of tetraethoxy-silane with P-amino Salicylic acid in benzene.

P-amino salicylic acid (7.657g, 0.05mol.) and tetraethoxy silane (21.6g, 0.104mol.) in benzene (60ml) were placed in a three neck round bottom flask equipped with a reflux condenser and a mechanical stirrer The mixture was heated to boiling and maintained at reflux for 8 hours. After 4 hours ethanol produced from the reaction was continuously distilled off with benzene at 78-80°C. The mixture was allowed tc cool then the yellowish-white solid was filtered off, washed several times with acetone and dried in vacuo over KOH. The yield was 9.21g, (57.16), m.p. 199-204°C (Decomp).



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Found C,52.10%; H,3.41%; N,8.12%; Si,5.59% $C_{21}H_{17}N_3O_9Si$ requires C,52.17%; H,3.52%; N,8.70%, 0,29.81%; Si,5.80%. The mass spectrum analysis showed the highest molecular ion peak at m/e 483. The pale yellowish-white crystalline compound is insoluble in most of the organic solvents.

Reaction of tetraethoxy-silane with P-amino Salicylic acid in tetrahydrofuran.

P-aminosalicylic acid (3.828g, 0.025mol.) and tetraethoxysilane (21.6g, 0.104mol.) in tetrahydrofuran (70ml.) were placed in a threee neck roundbottom flask equipped with a reflux condenser and a me-

chanical stirrer. The mixture was heated to boiling and maintained at reflux for 5 hours. After 2½ hours, the ethanol produced from the reaction and tetrahydrofuran were continuously distilled off at 65-69°C The light yellowish-white solid left in the flask was filtered off, washed several times with acetone, tetrahydrofuran and finally dried in vacuo. The yield was 6.57g, (67.94%), M.P. 198-203°C (Decomp.).

Found: C,52.12%. H,3.49%; N,8.22%; Si,5.53%. $C_{21}H_{17}N_3O_9Si$ requires C,52,17%; H,3.52%; N,8.70%; O,29.81%; Si,5.80%.

Molecular ion peak at m/e 484. The infra-red spectra of the two solids in nujol mull showed strong double absorption bands characteristic of NH_2 at 3450 and 3350cm^{-1} respectively. There is another strong NH-band at 1650cm-1. The large carboxylic acid OH-band absorbed at 3100, while the phenolic OH-band is observed at 1200cm-^{1}. a strong C-O absorption at 1650cm.$^{-1}$ and the SiO_4 and at 830cm^{-1}. Observation showed that the missing absorption bands at 765 and 1213cm-1 can be attributed to a SiNSi and SiNH.

The elemental, infra-red spectra, and mass spectra analyses have shown the two compounds obtained in benzene and tetrahydrofuran media to be identical.

(iii) Reaction of Silicon tetrachloride with Salicylic Acid in tetraethoxy-silane

To a stirred solution of Salicylic acid (6.9g 0.05 mol)in silicon tetrachloride (8.5g, 0.05mol.) in tetraethoxysilane (100ml.) under argon at 25°C. Reaction was observed to have started at 25°C before the reaction flask was heated in an oil bath at constant temperature of 130-140°C for 15 hours. The yellow suspension was filtared

The infra-red spectrum of the yellow filtrate showed a strong carbonyl absorption band VC=O at 1765cm-1; the C-H absorptions of the CH3 at 2995s and 2940s cm-1 and the CH2- band at 2915 w. cm^{-1}; and finally the SiO4 bands at 776m and 813cm^{-1} respectively.

The filterate examined by g.l.c. using a column packed with 15% carbonwax on universal support B at 90oC showed the presence of a single product apart from diethoxydichlorosilane and tetraethoxysilane peaks. The g.c. – mass spectrum showed the molecular ion at m/e 254. The yellow filtrate after distillation under low pressure at 122-126°C/3mm. yielded 5.43g of oily liquid.

Found: C,51.33%. H,5.55%. Si,10.98%

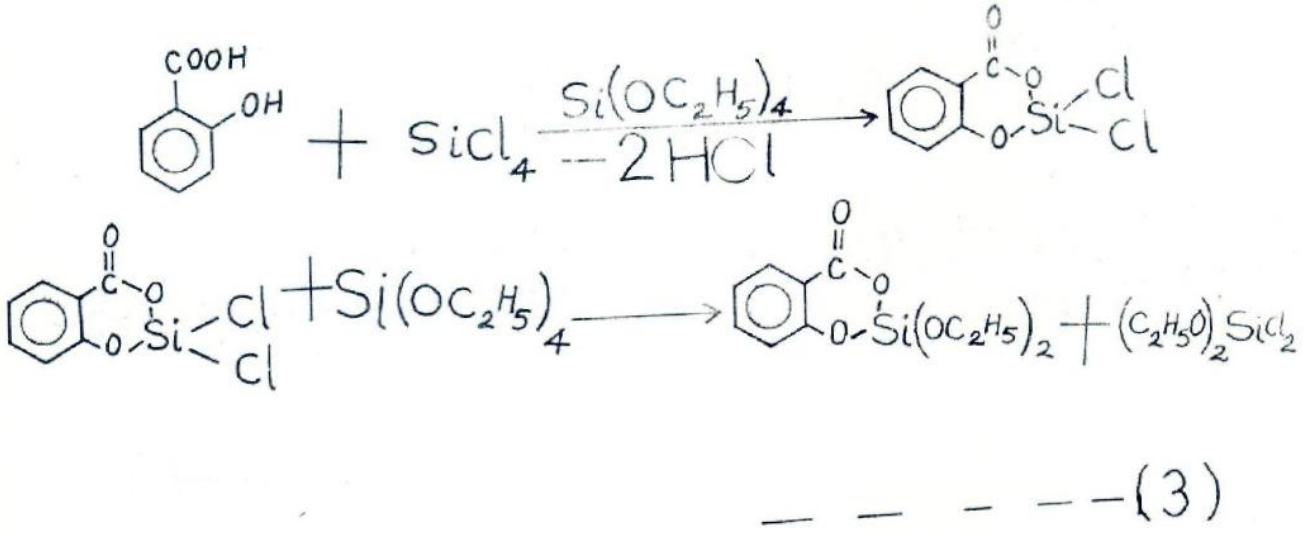
$C_{11}H_{14}O_5Si$ requires C, 51.97%; H,5.51%; 0.31.5% Si,11.02%.

iv. Reaction of benzoic acid with tetraethoxy-silane in toluene

Benzoic acid (6,18g. 0.051mol.) and tetraethoxysilane (22.42g, 0.11mol.) in toluene (80ml.) were placed in three-neck flask equipped with a reflux condenser and a mechanical stirrer. The mixture was heated to boiling and maintained at reflux for 7½ hours. After 4 hours the ethanol produced from the reaction was the lowest boiling fraction (78-80oC) followed by toluene at 109-111°C were continuously distilled off. The liquid product obtained was distilled to remove excess of unreacted tetraethoxysilane leaving 8.25g of oil residue, b.p. 128-130oC/4mm. The liquid compound is soluble in benzene and toluene and it can easily be hydrolysed.

Found: C,54 56%; H,6.92%. Si,9.23%.

$C_{13}H_{20}SiO_5$ requires C,54.93%; H,7.04%; 0,28.17% Si,9.86% The g.c. - mass spectrum showed the molecular ion at m/e 285. The infra-red spectrum of the oily liquid showed some characteristic absorption bands, strong CH_3-bands at 2995 and 2960 cm^{-1}, a strong carbonyl C=O absorption at 1720cm^{-1}; the SiO_4 bands at 790m and 803m. cm-1, respectively.



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