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Synthesis of Methylsilyl Derivates of Procaine and Their Diffusion Rates from an Ointment Base

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Four new methylsilyl and silicon compounds of procaine have been synthesised. Unlike procaine, the trimethylsilyl derivative was readily soluble in olive and vegetable oils at room temperature. The dimethylsilyl, methylsilyl and silicon derivatives were soluble in dioxane, carbon tetrachloride and benzene. The rates of diffusion of the four derivatives from an ointment base (lanoline, vaseline) into water were studied. The highest rate was exhibited by procaine and the lowest by its dimethylsilyl derivative. The LD_{100} of the trimethylsilyl derivative when administered subcutaneously in olive oil to rats was 1.25 g/kg.

Synthese von Methylsilylderivaten des Procains und Bestimmung ihrer Diffusionsraten aus Salbengrundlagen

Vier neue Methylsilyl- bzw. Silicon-Derivate des Procains wurden synthetisiert. Eine der neuen Verbindungen, das Trimethylsilylprocain, ist leicht fettlöslich. Das Dimethylsilyl-, Monomethylsilyl- und das Silicon-Derivat lösen sich in organischen Lösungsmitteln (Dioxan, Benzol und Tetrachlorkohlenstoff). Die Diffusionsraten der vier neuen Verbindungen aus einer Lanolin-Vaseline-Salbengrundlage sowie die akute Toxizität des Trimethylsilylderivates an Ratten wurden bestimmt.

It had been reported that silylation of the local anaesthetic agents benzocaine[1] and xylocaine[2] enhanced markedly their lipophilicity. Both the trimethylsilylbenzocaine and xylocaine derivatives were reported to be soluble in vegetable oils at ambient temperature and were easily diffused from a lipophilic base into water. These findings encouraged us to extend our studies to another significant anaesthetic agent – procaine base (Novocaine®, Polocaine®). This molecule possesses hydrogen atoms on nitrogen in the $-NH_2-$ group accessible to silylation.

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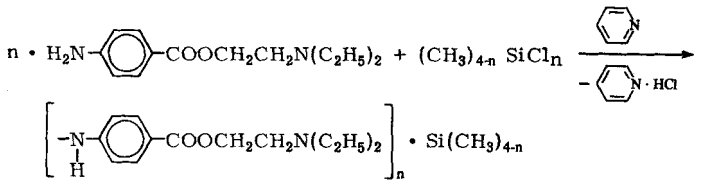
The organosilicon compounds were obtained by the following general reaction route:



where n = 1, 2, 3 and 4 are characterised by the presence or absence of hydrogen bonding which renders them more lipophilic than the parent compound. On the other hand, a poor hydrolytic stability of the Si-N linkage makes the derivatives interesting as prodrugs. They are likely to penetrate easily across lipophilic membranes and to be gradually hydrolysed in the body fluids to liberate procaine base. Procaine apart from its local anaesthetic activity also has other pharmacological activities e.g. as analgesic agent.

The objective of this work was to synthesise methylsilyl and silicon derivatives (n = 1, 2, 3, 4) of procaine and to study their diffusion rates from an ointment base. The pharmacological screening of the drugs were also carried out on rats.

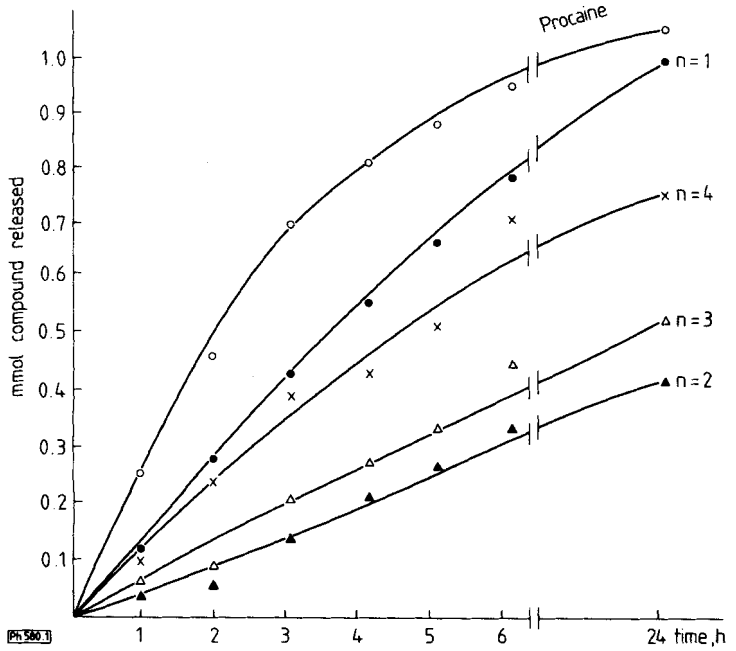


Fig. 1: Diffusion rates of trimethylsilyl derivatives of Procaine base from an ointment base (lanoline-vaseline) at 37 ± 0.5 °C.

Results and Discussion

The diffusion characteristics of procaine base and its derivatives are shown in Fig. 1 below.

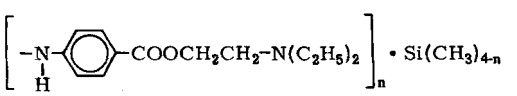
When considering the diffusion rates on the basis of molar concentrations of the procaine-silicon compounds, the highest rate was exhibited by procaine base itself, followed by its trimethylsilylamino derivative (Fig. 1). It was very significant to note that the diffusion rates of the silicon-, dimethylsilyl- and methylsilyl-derivatives of procaine base differ slightly, especially during the first four hours of experiments.

Considering the data shown in Fig. 1, it must be remembered that one mole of the silicon compound, $Si(N\text{-}Ar)_4$, when hydrolysed in aqueous medium liberated four moles of the parent compound procaine base and also $CH_3Si(N\text{-}Ar)_3$ liberated three moles of corresponding procaine base and so on. However, the number of moles of procaine base released in the form of a silicon- or methylsilyl-derivative from an ointment base was greater.

The conclusion can be drawn from these experiments that silylation of procaine base offers possibilities of obtaining a variety of derivatives with different diffusion rates. These derivatives behave like typical prodrugs.

Table 1: *Elemental Analyses and IR bands*

Molecular Formula n =		Molecular weight		C (%)		H (%)		N (%)		Si (%)		ν_{max} cm^{-1} Si-N ν_{as}
		Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	
1	$C_{16}H_{28}N_2O_2Si$	308.1	308	62.3	62.1	9.09	8.99	9.1	9.1	9.1	9.1	3312 S, 845 VS
2	$C_{28}H_{44}N_4O_4Si$	528.1	529	63.6	63.5	8.33	8.09	10.6	10.6	5.3	5.3	3380 S, 847 VS
3	$C_{40}H_{60}N_6O_6Si$	748.1	748	64.1	64.4	8.02	7.95	11.2	11.3	3.8	3.8	3425 M, 846 VS
4	$C_{52}H_{76}N_8O_8Si$	968.1	969	64.5	64.7	7.85	7.79	11.6	11.3	2.9	2.9	3397 S, 849 VS



In the IR spectra of compounds (n = 1, 2, 3) the absorptions due to C-H stretching at 2955 cm^{-1} was strongly amplified due to the replacement of hydrogen atom by methylsilyl groups. Absorption band due to ν_s Si-N was generally weak except in the case of compounds (n = 1, 2, 3, 4) having strong absorption bands due to ν_s Si-NH. The IR

spectrum was interpreted based on that of the procaine base and on literature data[4,5,6].

We thank Prof. *R. Horsted* and his co-workers of the Department of Physiological Sciences, Reading University, England, for their assistance with the pharmacological investigations.

Experimental Part

The ointment base was made up of equal parts of anhydrous vaseline and lanoline (unguentum molle).

IR spectra: Perkin Elmer spectrophotometer (model 157G), KBr plates. *Silicon content:* gravimetrically as silicon dioxide by the method of *Vogel*[3]. *Mass spectra:* A.E.I. mass spectrometer (model M.S. 12) with gas chromatograph.

Reaction of procaine with trimethylchlorosilane

To a stirred solution of 4.736 g (0.02 mol) procaine in a mixture of 1.58 g (0.02 mol) pyridine and 150 ml toluene was added slowly from a dropping funnel 17.38 (0.16 mol) trimethylchlorosilane at 20 °C under argon. The reaction flask was heated in an oil bath at reflux for 8 h. The white precipitate produced during the reaction was identified as pyridine hydrochloride. The yellow filtrate was first distilled to remove the solvents and then i. vac. The light yellow liquid obtained after distillation yielded 5.32 g, 86.3 %, b.p.$_3$ 182–184 °C. The molecular ion peak at m/e 308 corresponded with the molecular formula $C_{16}H_{28}N_2O_2Si$ of N,N′-diethylaminoethyl-p-aminobenzoxytrimethylsilane (n = 1). (See Table 1).

Reaction of procaine with dimethyldichlorosilane

To a stirred solution of 4.73 g (0.02 mol.) procaine in a mixture of 1.58 g (0.02 mol.) pyridine and 150 ml toluene was added slowly from a dropping funnel 1.291 g (0.01 mol.) dimethyldichlorosilane at 20 °C under argon. The reaction flask was heated in an oil bath at reflux for 13 h. The white precipitate of pyridine hydrochloride produced was filtered hot while the filtrate was allowed to cool. White crystalline precipitates were precipitated out on addition of dry petroleum ether (b.p. 60–80 °C). The precipitates were recrystallised from ethanol, yield 3.25 g, 61.8 % m.p. 175–178 °C.

The ms of the crystals showed the highest molecular ion peak at m/e 529: bis(N,N^1-diethylamino-ethyl-p-aminobenzoxy)dimethylsilane (n=2).

Reaction of procaine with methyltrichlorosilane

To a stirred solution of 7.09 g (0.03 mol) procaine in a mixture of 2.37 g (0.03 mol) pyridine and 250 ml toluene was added slowly from a dropping funnel 1.5 g (0.01 mol) methyltrichlorosilane at 20 °C under argon. The reaction flask was heated in an oil bath at reflux for 16 h. After filtering off the pyridine hydrochloride precipitate, the filtrate was also treated with petroleum ether (b.p. 60–80 °C) and white crystalline substance precipitated out. Recrystallised from ethanol, yield 5.24 g, 44.52 %, m.p. 184–186 °C.

The molecular ion peak of the compound at m/e 748 corresponded with the molecular formula $C_{40}H_{60}N_6O_6Si$ of tris(N,N^1-diethylaminoethyl-p-aminobenzoxy)methylsilane (n = 3).

Reaction of procaine with tetrachlorosilane

To a stirred solution of 47.26 g (0.2 mol) procaine in a mixture of 15.8 g (0.2 mol) pyridine and 250 ml toluene was added slowly from a dropping funnel 8.51 g (0.05 mol) tetrachlorosilane in 50 ml toluene

at 20 °C under argon. The reaction flask was heated in an oil bath at reflux for 19 h. After filtering off the pyridine hydrochloride, the filtrate was treated in a similar manner as described above. The white crystalline solid yielded 23.1 g, 47.96 %, m.p. 191–193 °C. The ms showed the highest molecular ion peak at m/e 969: tetra(N,N'-diethylaminoethyl-p-aminobenzoxy)silane $C_{52}H_{76}N_8O_8Si$ (n = 4).

Pharmacology

Acute Toxicity

The acute toxicity of the trimethylsilyl derivative of procaine base was identified in three rats (rats weighed, 240, 310, and 340 g) which were given subcutaneously as a 50 % solution of the compound in olive oil. The mean LD_{100} value was 1.25 g/kg. Olive oil was non toxic when tested.

Measurement of diffusion rates

Ointments were prepared on a molar basis by trituration. Each specimen is made up of 5 mmol of a substance and 15 g of the vehicle. The diffusion rate across a cellophane membrane (40 g/ml) into a 10 % NaOH solution, or into water was measured at 37 ± 0.5 °C using a method designed by *Mutimer* et al[7]. The surface area of the membrane was 100 cm^2 and the vol. of sodium hydroxide solution or water was 80 ml. The ointment layer was 1.1 mm thick. At intervals of 1 h, 10 ml aliquot was pipetted out from the beaker and replaced with equal vol. of sodium hydroxide solution or water.

The determination of procaine base which was released from a silyl derivative on hydrolysis with water or alkali solution was carried out alkalimetrically using a method outlined in Brit. 1973[8].

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