International Journal of Pharmaceutics, 28 (1986) 1–9
Elsevier

IJP 00931

Review Article

Prodrugs utilizing a reversible silyl linkage

J.S. Millership and M.L. Shanks

Department of Pharmacy, Queen's University of Belfast, Medical Biology Centre, Belfast BT9 7BL, Northern Ireland (U.K.)

(Accepted August 1st, 1985)

Key words: pro-drugs – drug latentiation – organosilicon compounds – silylation

Harper is credited with introducing the term "drug latentiation" to describe the conversion of a drug molecule into a derivative from which the parent drug molecule can be regenerated in vivo (Harper, 1959). He defined the term drug latentiation as: "The chemical modification of a biologically active compound to form a new compound which upon in vivo enzymatic attack will liberate the parent compound".

This definition was subsequently modified by Kupchan et al. (1965) to include non-enzymatic attack for the liberation of the parent compound. The term pro-drug is used to include latentiated drug derivatives along with substances that are converted, after administration, into the actual substances which elicit a pharmacological response (Sinkula and Yalkowski, 1975). There are many examples of the application of the pro-drug approach to the improvement of drug delivery and various reviews have been presented on the general topic (Harper, 1962; Ariens, 1966; Notari, 1973; Sinkula and Yalkowski, 1975; Higuchi and Stella, 1975). Von Daehme et al. (1970a and b) have, for example, studied the utilization of acyloxymethyl esters of ampicillin and demonstrated the excellent properties of pivaloyloxymethyl ampicillin in terms of absorption and rapid regeneration of the parent ampicillin. Bungaard et al. (1984) have investigated the use of amino acid esters of metronidazole in an attempt to overcome the low aqueous solubility of the parent compound. Their results indicated that the N,N-dimethylglycinate ester (hydrochloride salt) was the most suitable pro-drug form of metronidazole for the formulation of parenteral solutions.

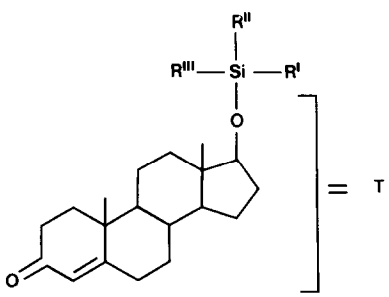
In both the above examples the reversible linkage was the alkyl ester group, this linkage being rapidly hydrolyzed in vivo. This linkage is probably the most utilized in drug latentiation; however, many other functional groups have been investigated, for example, ethers, enol ethers, azides, amides and phosphate esters. The main requirement for the reversible linkage, once it has served its purpose (i.e. improving aqueous solubility, increasing absorption, etc.), is that it should rapidly release the parent compound. The Si–O linkage of certain silyl ethers and esters is known to be easily broken under a variety of mild hydrolytic conditions and thus a number of workers have investigated the use of organosilyl ethers and esters as potential reversible derivatives for drug latentiation. Trimethylsilylation has been used extensively for derivatization purposes in GLC (Pierce, 1968). These derivatives are ideal for GLC in that generally they are easily prepared, thermally stable and more volatile than the parent compound. Trimethylsilyl derivatives of hydroxyl, carboxyl and amino functionalities have been

Correspondence: J.S. Millership, Department of Pharmacy, Queen's University of Belfast, Medical Biology Centre, 97 Lisburn Road, Belfast BT9 7BL, Northern Ireland, U.K.

widely used in drug analysis by GLC. The one drawback with trimethylsilyl derivatives is the hydrolytic instability in the presence of moisture. Trimethylsilyl and other organosilyl derivatives have been used as protecting groups in synthetic medicinal chemistry, the *t*-butyldimethylsilyl group has been used for the protection of hydroxyl functionalities in the synthesis of prostaglandin precursors (Corey and Venkateswarlu, 1972). This group is approximately 10^4 times more stable to acidic or basic solvolysis than the trimethylsilyl group; it is, however, selectively and rapidly cleaved by tetra-*n*-butylammonium fluoride. Thus organosilyl derivatives have been used extensively in drug analysis and synthesis; the utilization of these organosilyl derivatives (of hydroxyl and carboxyl functionalities) as potential latentiating groups is now reviewed.

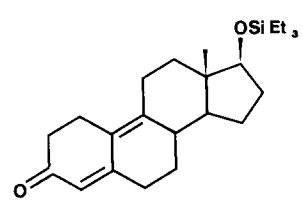
Steroids

A number of workers have investigated the androgenic and myotrophic activity of organosilicon derivatives of testosterones. Chang and Jain (1966) reported the synthesis and biological evaluation of six testosteroxysilanes, the structures of which are detailed below.



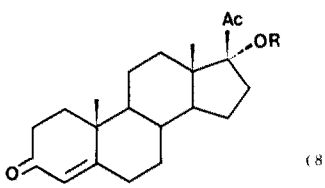
	R	R	R
(1)	CH_3	CH_3	CH_3
(2)	CH_3	CH_3	T
(3)	CH_3	T	T
(4)	C_6H_5	C_6H_5	C_6H_5
(5)	C_6H_5	C_6H_5	T
(6)	C_6H_5	T	T

The testosteroxysilanes were prepared by the reaction of testosterone with the corresponding methylchloro- or phenylchlorosilane in benzene with pyridine as the base. These compounds were all shown to be less polar than testosterone itself by means of partition paper chromatography. The bioassay of these compounds, in the rat, involved the determination of the androgenic and myotrophic activity using testosterone as a standard. The results indicated that only testosteroxytrimethylsilane (1) possessed significant androgenic or myotrophic activity over the 7-day period of the experiment. Saunders (1966) has also investigated the androgenic and myotrophic activity of testosteroxytrimethylsilane (1) in the rat. In this work these activities were studied over a 50-day period with testosterone propionate as the standard. These results showed that the maximal androgenic activity of testosterone propionate (as measured by the weights of the seminal vesicles and ventral prostate) was observed between seven and ten days, whereas with testosteroxytrimethylsilane (1) the maximal activity occurred between 20 and 30 days. The level of the effect was greater in the case of testosteroxytrimethylsilane (1) and the effectiveness lasted for a longer period. The myotrophic activity of testosteroxytrimethylsilane (1) was prolonged but the stimulatory effect on the levator ani muscle was less dramatic than the effects on the seminal vesicles and the ventral prostate. Minailova et al. (1976) described the synthesis of a series of triethylsilyl ethers of 17β-hydroxy steroids and also reported on the testing of these compounds for androgenic and myotrophic activity. All the compounds demonstrated androgenic and myotrophic activity when given orally but only 17β-triethyl-

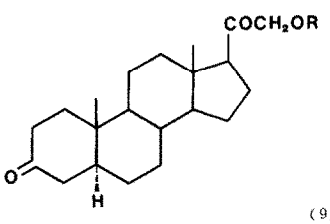


(7)

silyloxy-4,9(10)-estradien-3-one (7) was more active than 17-methyltestosterone. When administered subcutaneously a number of the compounds showed no activity and only 17β-triethylsilylloxy-4,9(10)-estradien-3-one (7) had greater myotrophic activity than testosterone. Golubovskaya and Pivnitskii (1976) reported the synthesis of 17α-trimethylsiloxyprogesterone (8) by treatment of 17α-hydroxyprogesterone with N,O-bis(trimethylsilyl) acetamide and chlorotrimethylsilane. The progestational activity of this silyl ether did not exceed that of progesterone when given i.m. and when given orally the activity was approximately equal to 17α-hydroxypregn-4-en-20-yn-3-one (ethisterone). Brown (1970) reported the preparation of a series of trimethylsilyloxy derivatives of 21-hydroxy-pregnane-3,20-diones. Thus the treatment of 21-hydroxy-5α-pregane-3,20-dione (9) with chlorotrimethylsilane and hexamethyldisilazane gave 21-(trimethylsiloxy)-5α-pregnane-3,20-dione (10). The silyl ethers prepared were found to possess anti-inflammatory and neoglycogenetic activity. The synthesis of 17-ethynylestra-1,3,5(10)-triene3,17-diol-3-trimethylsilylmethylether (11) has been reported (Barcza, 1971). This compound was reported to possess oestrogenic activity when given to rats; this compound is not in fact a silyl ether but a methylsilyl ether and thus the hydrolytic stability will be greater. The reported long-term oestrogenic activity of the compound does, however, suggest that it is acting as a latentiated derivative. Fessenden and Fessenden (1980) suggest that although these types of compound are hydrolytically stable they may not necessarily be stable to metabolic hydrolysis. There are two reports of the investigation of norithisterone pentamethyldisiloxy ether (12) as a possible long-acting contraceptive agent (Naderi and Fotherby, 1983; Watson et al., 1983). Naderi and Fotherby (1983) studied the in vitro hydrolysis (using a rabbit liver preparation) of a series of esters of norethisterone including norethisterone pentamethyldisiloxy ether (12). These workers reported no observable hydrolysis of norethisterone pentamethyldisiloxy ether (12) under the conditions used. Watson et al. (1983) reported that in biological testing of norethisterone pentamethyldisiloxy ether (12) there was no prolongation of contraceptive activity com-

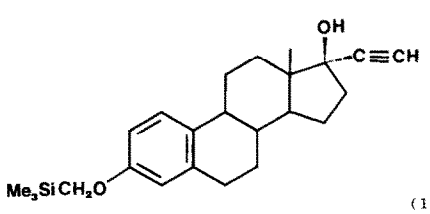


(8) R = $SiMe_3$

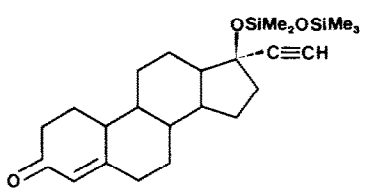


(9) R = H

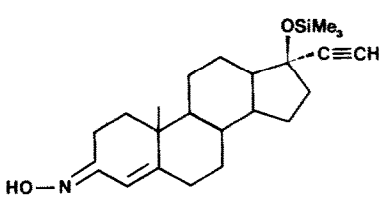
(10) R = $SiMe_3$



(11)



(12)



(13)

pared to the control which in this case was norethisterone enanthate.

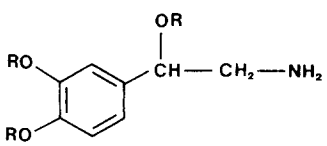
Zhao et al. (1981) prepared a series of steroid oximes and derivatives thereof, amongst these derivatives the oxime of 19-nor-17α-ethinyl-17β-silyloxy-androstan-3-one (13) was reported to show significant early pregnancy terminating properties.

Sympathomimetic amines

Crevling et al. (1969) investigated a series of latentiated derivatives of noradrenaline. These workers prepared [7-^{3}H]3,4,β-triacetylnoradrenaline (15) and [7-^{3}H]3,4,β-Tris(trimethylsilyl) noradrenaline (16) from [7-^{3}H]noradrenaline (14).

Trace amounts of the radiolabelled compounds were administered i.v. to mice in a mixture of dimethylsulphoxide and isotonic sodium chloride (11 : 1, 0.1 ml). Table 1 shows the distribution of the radioactivity between the brain and heart following administration. From these results it can be seen that the derivatives 15 and 16 readily entered the CNS; however, both derivatives survived for long periods in the brain showing little tendency to revert to the parent noradrenaline. Crevling et al. (1969) concluded that these derivatives may be useful in providing the CNS with a sustained release form of noradrenaline.

Pinder (1970) proposed that 3,4-diacetyl- and 3,4-bis(trimethylsilyl)-derivatives of dopamine might be useful latentiated forms of dopamine for the treatment of Parkinsonism although no synthetic or biological data were presented to substantiate this hypothesis. Gerlach et al. (1983) have



(14) R = H

(15) R = Ac

(16) R = SiMe$_3$

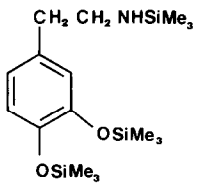
TABLE 1

DISTRIBUTION OF RADIOACTIVITY BETWEEN BRAIN AND HEART AFTER ADMINISTRATION OF [^{3}H]NORADRENALINE; [^{3}H]3,4,β-TRIACETYLNORADRENALINE AND [^{3}H]3,4,β-TRIS(TRIMETHYLSILYL) NORADRENALINE

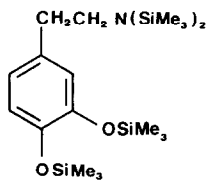
Compound	Activity (μCi)		Ratio heart/brain
	Heart	Brain	
[^{3}H]Noradrenaline	7.3	0.4	18.3
[^{3}H]3,4,β-Triacetyl-noradrenaline	0.07	0.05	1.2
[^{3}H]3,4,β-Tris-(trimethylsilyl)noradrenaline	0.06	0.10	0.60

synthesized N-trimethylsilyl-3,4-bis(trimethylsilyloxy)-2-phenyl-ethylamine (17) and N,N-bis(trimethylsilyl)-3,4-bis(trimethylsilyloxy)-2-phenyl-ethylamine (18). These compounds were shown to have increased lipophilicity compared to dopamine and also to positively influence the rigid akinetic syndrome induced by reserpine when tested in rats.

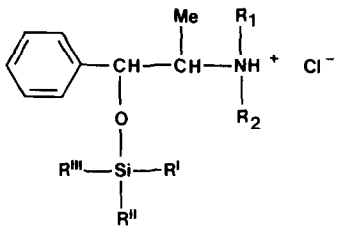
Beckett et al. (1975) investigated a series of trialkylsilyl derivatives of the amino alcohols, methylephedrine (19), ephedrine (20) and norephedrine (21); examples are shown below. The



(17)



(18)

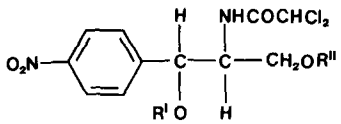


(19) $R_1 = R_2 = H$

(20) $R_1 = H$, $R_2 = Me$

(21) $R_1 = R_2 = Me$

R , R , R = Me, Et, Pr etc.



(22) R = R = H

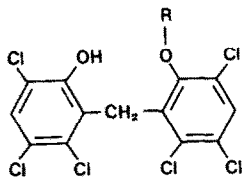
(23) R = R = Si $(Alk)_3$

(24) R = R = $Si(Ph)_3$

hydrolysis rates of the silyl derivatives were determined in McIlvaines phosphate-citrate buffer pH 4.0 or 7.4. The results of this work indicated that the rates of hydrolysis were dependent on both the number and type of alkyl substituents on the silicon atom. The partition coefficients of the derivatives were measured in a heptane/water system, substitution of additional methylene units onto the silicon atom resulting in an increase in the log P value by 0.5 of a log P unit. The authors proposed that by modifying the trialkylsilyl moiety, the partition coefficients of the derivatives and the hydrolysis rates (to the parent compound) could be controlled. They deduced that the enhanced lipophilicity conferred on the molecule by introduction of the silyl functionality would affect transfer across lipid barriers in vivo and once in the biophase the silyl derivative would hydrolyze to the parent drug molecule. Knowledge of such factors would then allow the design of molecules in such a way as to control the pharmacokinetic parameters.

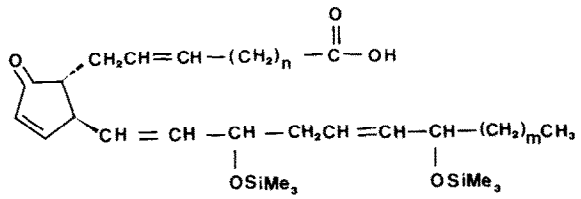
Antimicrobial agents

Chloramphenicol (22) was in the past used as a broad-spectrum antibiotic; however, it suffered from a noticeably bitter taste and also there was a problem in obtaining sufficiently prolonged blood levels of the active substance following parenteral administration. Upjohn have patented a series of silyl derivatives of chloramphenicol (Upjohn, 1968; Houtman, 1969). The bis(trialkylsilyl)- (23) and bis(triarylsilyl)- (24) derivatives were prepared by reacting chloramphenicol with an excess of the appropriate trialkyl (aryl) silyl chloride in pyridine. The monosubstituted derivatives (where R_1 is the silyl functionality and R_2 is hydrogen) were readily prepared by mild acid hydrolysis of the disubstituted compounds. The patents claim that these derivatives are far less bitter than the parent compound and superior in terms of activity. The CD_{50} versus *Pasturella mulocida* (subcutaneously in mice) of the bis(trimethylsilyl)-derivative was reported as 21 mg/kg (equivalent 15 mg/kg of base) which is reported as being substantially superior to the chloramphenicol control. Hexachlorophene (25), a phenolic bactericide, is predominantly active against Gram-positive bacteria especially *Staphylococci,* however, it exhibits low activity against Gram-negative bacteria especially *Escherichia coli.* An organosilicon derivative of hexachlorophene (26) was synthesized (Schwarz Services Int. Ltd., 1975) and found to be effective against *E. coli* in vitro. The activity of this compound (26) against Gram-positive bacteria was lower than that of hexaclorophene; however, the derivitization appears to have broadened the antibacterial spectrum. Allen and Watson (1966) have reported the synthesis of a number of diphenoxy diethoxysilanes which slowly hydrolyze in a sustained manner on contact with water. This hydrolysis releases the bacterial and/or fungicidal phenol; however, the application relates specifically to the treatment of textiles.



(25) R = H

(26) R = $Si(OEt)_2(CH_2)_3NH_2$



(27) n = 2, m = 1

Prostaglandins

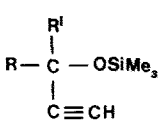
The synthesis of a series of silyl ethers of several prostaglandins has been described (Anderson and Weinschenker, 1973). The derivatives were reported to possess valuable pharmacological properties as modifiers of smooth muscle activity, gastric secretion, blood pressure, lipolysis and the reproductive system in laboratory animals. The silicon–oxygen bond of the silyl ethers was shown to be hydrolyzed under physiological conditions thereby liberating the parent prostaglandin; thus the silyl derivatives are acting as latentiated derivatives.

11,15(S)-Bis(trimethylsilyloxy)-9-oxo-5-cis,13-trans-prostadienoic acid(27) a pro-drug of the corresponding prostaglandin was found to be particularly useful in treating hyperacidity when tested in rats. At pH 2 to 4 this silyl ether hydrolyzed to give the parent prostaglandin which inhibits gastric secretion. As the pH of the stomach reaches pH 4.5–5 the hydrolysis of the silyl ether is reduced and the unchanged silyl ether passes into the intestine without causing increased intestinal motility with resultant diarrhoea (as would the parent prostaglandin).

Sedatives and hypnotics

Millership and O'Hare (1976) investigated the effects of the introduction of the trimethylsilyl moiety on the physicochemical properties of a series of ethinyl alcohols with established CNS depressant activity. The compounds investigated are shown below. The approach of this study was based on two factors. Firstly that the trimethylsilyl ethers should have increased lipophilicity in comparison to the parent alcohols and secondly that the silyl derivatives would undergo facile hydrolysis to the parent alcohols. The partition coefficients of the parent alcohols and their silyl derivatives were measured in the octanol/water system. The increase in the log P value due to the introduction of the trimethylsilyl functionality was of the order of 0.5–0.6. The authors also investigated the stability of the silyl derivatives in a variety of test systems. The results indicated that the silyl derivatives were suitable for consideration as latentiated derivatives. O'Hare (1981) assessed the biological activities of the ethinyl alcohols and their trimethylsilyl derivatives by administration of the test compounds to mice and the ED_{50} values for hypnotic activity were determined. A comparison of the results for 3-methylpentyn-3-ol and the corresponding trimethylsilyl ether are presented in Table 2.

These results indicated that the silyl ether behaves very similarly to the parent compound when



	R	R
(28)	H	C_3H_7
(29)	CH_3	C_2H_5
(30)	-- $(CH_2)_4$ --	
(31)	-- $(CH_2)_5$ --	

TABLE 2

HYPNOTIC ACTIVITY OF 3-METHYLPENTYN-3-OL AND 3-METHYLPENTYN-3-OL TRIMETHYLSILYL ETHER

	Parent alcohol		Silyl ether		
	Oral	s.c.	Oral	s.c.	s.c.
Dose	304 mg/kg (ED_{50})	304 mg/kg (ED_{50})	520 mg/kg [a]	520 mg/kg	715 mg/kg (ED_{50})
Effect	Hypnosis	Hypnosis	Hypnosis	Sedation	Hypnosis
Time for onset	15 min	23 min	20.4 min	15 min	29.3 min
Duration of activity	6.4 h	6.6 h	5.6 h	7.8 h	11 h

[a] Equimolar with 304 mg/kg of parent alcohol.

given orally; however, when equivalent doses are given subcutaneously the silyl ether does not cause hypnosis but only sedation. The ED_{50} (hypnotic) dose of the silyl ether (subcutaneous) does, however, produce a longer duration of hypnosis although the time for onset is approximately twice as long as that of the parent compound.

Anticancer agents

Chiu et al. (1982) have studied a number of N- and O-triorganosilyl derivatives of known oncostatic agents as potential pro-drugs. O-(*t*-butyldimethylsilyl)chlorambucil and several O-(triorganosilyl)carbamate derivatives of nor-nitrogen mustards showed significant activity against P-388 lymphocytic leukemia in mice. O-Tribenzylsilyl-N,N-bis(2-chloroethyl)carbamate (32) was especially encouraging in the screening tests and has been selected for further evaluation by the National Cancer Institute in its tumor panel testing program.

A series of compounds described as polyorganosilsesquioxanes have been reported to possess antitumor activity (Tokuyama Soda Co. Ltd., 1981). Thus $O_{1.5}Si(CH_2)_3NHCH_2CH_2CN$ (400 mg/kg/day i.p. for 9 days) given to mice, bearing Erlich ascites tumor, increased the animals survival time by 52%. Here, once again, there is no clear indication of the actual nature of the active agent.

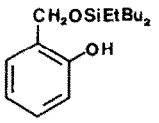
$(ClCH_2CH_2)_2N-\overset{\overset{O}{\|}}{C}-OSiBz_3$

(32)

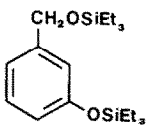
Silicon derivatives with modified diffusion rates

Piekos and co-workers (Piekos et al., 1976a and b; Piekos et al., 1977) have described the synthesis of a number of silicon derivatives of pharmaceutical substances containing a phenol group. The release rates of these silicon derivatives from an ointment base was then compared to the parent phenols. Piekos et al. (1976a) reported the synthesis of methylsilyl and silicon derivatives of phenol and *ortho-*, *meta-* and *para*-cresols by reaction of these compounds with chlorotrimethylsilane, dichlorodimethylsilane, methyltrichlorosilane and silicon tetrachloride. The general formula for these compounds is $(CH_3)_{4-n}Si(OPh)_n$ where n = 1, 2, 3 or 4 and Ph = C_6H_5 or $C_6H_4CH_3$.

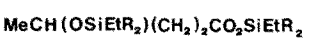
The diffusion rates of these compounds from an ointment base (equal parts anhydrous vaseline and lanolin) were then studied using a dialysis device with a cellophane membrane. All four trimethylsilyl derivatives had increased diffusion rates compared to the parent compounds. The cresol derivatives diffused faster than the phenol derivative and the order of diffusion for the cresol derivatives was *para* > *meta* > *ortho*. The dimethylsilyl, methylsilyl and silicon derivatives of phenol all diffused more slowly than phenol itself whilst the corresponding



(33)



(34)



(35)

cresol derivatives displayed equivalent or faster diffusion rates compared to the parent compounds. Similar investigations were then carried out on the methylsilyl and silicon derivatives of thymol and guaiacol (Piekos et al., 1976b) and carvacrol (Piekos et al., 1977). In all cases the diffusion rates of the derivatives, from vaseline-lanolin ointment base, were slower than that of the parent phenol and the diffusion rates were markedly influenced by the nature of the substituent on the phenol ring.

Analgesics and anti-inflammatories

Lapkin et al. (1981a and b; 1983) have reported various silyl derivatives possessing analgesic and anti-inflammatory activity, these compounds include (2-hydroxybenzyloxy) ethyldibutylsilane (33), (3-triethylsilyloxybenzyloxy)triethylsilane (34) (Lapkin et al., 1981a) and trialkylsilyl-γ-(trialkylsilyloxy)valerates (35a and b) (Lapkin et al. 1981b). A series of compounds including trialkylsilyloxy acids and ketones have been synthesised (Lapkin et al. 1983). These compounds, when tested in rats and mice, were reported to possess analgesic and anti-inflammatory activity.

Toxicity

One problem that must always be considered when producing latentiated drug derivatives is that breaking the reversible linkage and release of the temporary transport moiety must not result in any toxic effects. The literature reported above, although discussing the breakdown of the reversible linkage and production of the parent compound, pays little heed to the silicon-containing portion of the molecule. The most likely outcome of the breakdown of organosilyl derivatives would be the formation of the corresponding organosilanol. In the case of the trimethylsilyl group this would result in the formation of trimethylsilanol which can rapidly self-condense to yield hexamethyldisiloxane (Rochow, 1946); with increasing substituent size the silanos become less prone to this self-condensation. No systematic investigation appears to have been carried out into the nature and toxicity of these breakdown products from organosilyl derivatives; however, compounds such as siloxanes are considered relatively free from toxicity.

This review has presented a survey of investigations into the uses of organosilyl derivatives as latentiated drug derivatives. Although, to the authors' knowledge, none of the above examples have become established as clinically useful drugs, the potential of these derivatives has been demonstrated. The last decade has seen the introduction of a number of latentiated drugs into the clinician's armoury, and with the continuing work on these organosilyl derivatives there may yet be clinically efficacious examples of these types of compounds.

References

Allen, T.C., and Watson, H.J., Haloarylsilanes. U.S. Patent (1966) 3,253,009.

Anderson, N.H. and Weinshenker, N.M., Pharmaceutical Compositions Comprising Alkylsilyl Ethers of Prostaglandins. U.S. Patent (1973) 3,764,677.

Ariens, E.J., Molecular pharmacology, a basis for drug design. In Progress in Drug Research, Vol. 10, Interscience Publishers, New York, 1966, pp. 429–529.

Barcza, A., Neue Steroid-Verbindungen und Verfahren zu deren Herstellung. German Offen. (1971) 2,100,967.

Beckett, A.H., Taylor, D.C. and Gorrod, J.W., Trialkylsilyl moieties as potential pharmacokinetic modifying groups for aminoalcohols. J. Pharm. Pharmacol., 27 (1975) 588–593.

Brown, E.A., Anti-inflammatory and neoglycogenetic 21-(trialkylsilyloxy)pregnane-3,20-diones. U.S. Patent (1970) 3,513,163.

Bundgaard, H., Larsen, C. and Thorbek, P., Prodrugs as drug delivery systems. XXVII. Preparation and enzymatic hydrolysis of various water soluble amino acid esters of metronidazole. Int. J. Pharm., 18 (1984) 67–77.

Chang, E. and Jain, V.K., Synthesis and properties of mono-, di- and tritestosteroxysilanes. J. Med. Chem., 9 (1966) 433–435.

Chiu, F.T., Chang, Y.H., Ozkan, G., Zon, G., Fitcher, K.C. and Phillips, L.R. Synthesis, hydrolytic reactivity, and anti-cancer evaluation of N- and O-triorganosilylated compounds as new types of potential prodrugs. J. Pharm. Sci., 71 (1982) 542–551.

Corey, E.J. and Venkateswarlu, A., Protection of hydroxyl groups as tert-butyldimethylsilyl derivatives. J. Am. Chem. Soc. 94 (1972) 6190–6191.

Crevling, C.R., Daly, J.W., Tokuyama, T. and Witkop, B., Labile lipophilic derivatives of norepinephrine capable of crossing the blood–brain barrier. Experientia, 15 (1969) 26–27.

Fessenden, R.J. and Fessenden, J.S., Trends in organosilicon biological research. Adv. Organometallic Chem., 18 (1980) 275–299.

Gerlach, M., Jutzi, P., Stasch, J.P. and Przuntek, H., Synthesis and pharmacological properties of silylated dopamines and 4,4-diphenylpiperidines. Z. Naturforsch., B: Anorg. Chem., Org. Chem. 38B (2) (1983) 237–242.

Golubovskaya, L.E. and Pivnitskii, K.K., Synthesis and gestagenic activity of a trimethylsilyl ether of 17α-hydroxyprogesterone Khim.-Farm. Zh. 10 (1976) 52–53; C.A. 85 (1976) 33260.

Harper, N.J., Drug latentiation. J. Med. Pharm. Chem., 1 (1959) 467–500.

Harper, N.J., Drug latentiation. In progress in Drug Research, Vol. 4, Interscience Publishers, New York (1962) 221–294.

Higuchi, T. and Stella, V., Pro-drugs as Novel Drug Delivery Systems, ACS Symposium Series 14, Am. Chem. Soc., Washington, DC (1975).

Houtman, R.L., Silyl Substituted Chloramphenicol. U.S. Patent (1969) 3,442,926.

Kupchan, S.M., Casy, A.F. and Swintosky, J.V., Drug latentiation, synthesis and preliminary evaluation of testosterone derivatives. J. Pharm. Sci., 54 (1965) 514–524.

Lapkin, I.I., Dvinskikh, V.V., Pidemskii, E.L. and Mardanova, L.G., Trialkylsilyl γ-(trialkylsiloxy)valerates with anti-inflammatory and analgesic activity. U.S.S.R. (1981a) 756,810; C.A. 95 (1981) 197761q.

Lapkin, I.I., Pidemskii, E.L., Mardanova, L.G. and Dvinskikh, V.V., Analgesic and anti-inflammatory action of some organosilicon compounds. Khim.-Farm. Zh. 15 (1981) 34–39; C.A. 95 (1981b) 73167f.

Lapkin, I.I., Pidemskii, E.L., Dvinskikh, V.V., Goleneva, A.F. and Mardanova, L.G., Anti-inflammatory and analgesic action of silicon containing esters and ketones. Khim.-Farm. Zh., 17 (1983) 294–298; C.A. 99 (1983) 151u.

Millership, J.S., and O'Hare, R.E., Trimethylsilylethers of ethinylalcohols as latentiated drugs. J. Pharm. Pharmacol., 28 (1976) 14p.

Minailova, O.N., Ivanenko, T.I., Rzheznikov, V.M. and Pivinitskii, K.K., Synthesis and biological activity of the triethylsilyl ethers of 17β-hydroxy steroids. Khim.-Farm. Zh., 10 (1976) 37–41; CA. 86 (1977) 12066q.

Naderi, S. and Fotherby, K., Long-acting contraceptive agents; in vitro hydrolysis of esters of norethisterone and levonorgestrel. Steroids, 41 (1983) 397–417.

Notari, R.E., Pharmacokinetics and molecular modification; implications in drug design and evaluation. J. Pharm. Sci., 62 (1973) 865–881.

O'Hare, E.R., Trimethylsilyl Ethers of Ethinylalcohols as Latentiated Drugs, Ph.D. Thesis, The Queen's University of Belfast, 1981.

Piekos, R., Teodorczyk, J. and Stozkowska, W., Silicon derivatives of medicinal agents. X. Diffusion rates of methylsilyl derivatives of isomeric cresols and phenol from an ointment base. Sci. Pharm., 44 (1976a) 13–18.

Piekos, R., Macholla, J., Sankowski, M. and Stozkowska, W., Silicon derivatives of medicinal agents. XII. Methylsilyl derivatives of thymol and guaiacol and their release rates from an ointment base. Sci. Pharm., 44 (1976b) 206–211.

Piekos, R., Stozkowska, W. and Sankowski, M., Silicon derivatives of medicinal agents. XIV. Methylsilyl derivatives of carvacrol and their release rates from an ointment base. Sci. Pharm., 44 (1977) 297–300.

Pierce, A.E., Silylation of Organic Compounds. Pierce Chemical Co., IL, 1968.

Pinder, R.M., Possible dopamine derivatives capable of crossing the blood–brain barrier in relation to parkinsonism. Nature (London), 228 (1970) 358.

Rochow, E.G., An Introduction to the Chemistry of the Silicones, Chapman Hall, London, 1946.

Saunders F.J., A singularly long-acting ether of testosterone. Proc. Soc. Exp. Biol. Med., 123 (1966) 303–304.

Schwarz Services Int. Ltd., Silanised antimicrobial compounds. German Offen. (1975) 2,538,341.

Sinkula, A.A. and Yalkowsky, S.H., Rationale for the design of biologically reversible drug derivatives — Prodrugs. J. Pharm. Sci., 64 (1975) 181–209.

Tokuyama Soda Co., Ltd., Polyorganosilsesquioxanes as neoplasm inhibitors. Jpn. Kokai Tokkyo Koho JP (1981) 81,110,622; C.A. 96 (1982) 15213c.

Upjohn, Improvements in or relating to Antibiotic Derivatives and the manufacture thereof. British Patent (1968) 1,129,240.

Von Daehme, W., Frederikson, E., Gundersen, E., Lund, F., Morch, P., Peterson, H., Roholt, K., Tybring, L. and Godtfredsen, W.O., Acyloxymethyl esters of ampicillin. J. Med. Chem., 13 (1970a) 607–612.

Von Daehme, W., Godtfredsen, W.O., Roholt, K., and Tybring, L., Pivampicillin, a new orally active ampicillin ester. Antimicrob. Agents Chemother., (1970b) 431–437.

Watson, T.G., Hosking, M., Herz, J.E., Torres, J.V., Muller, J., Murillo, A., Cruz, S., Shafiee, A., Vossoghi, M., Savabi, F., Sotheeswaren, S. and Puvanesarajah, V., Long-Acting contraceptive agents: esters of norethisterone with α- and/or β-chain branching. Steroids, 41 (1983) 255–265.

Zhao, Z., Li, W., Li, D. and Wu, X., Study on steroid oximes (1). Synthesis and biological evaluation of forty-three compounds. Shengzhi Yu Piyun, 1 (1981) 24–30. C.A.; 97 (1982) 39219f.