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Trialkylsilyl moieties as potential pharmacokinetic modifying groups for aminoalcohols

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Water soluble derivatives of the aminoalcohols methylephedrine, ephedrine and norephedrine have been synthesized to contain various trialkyl silyl groups attached to the hydroxyl group of the aminoalcohol hydrochloride. Variation of the alkyl substituents on the silyl group produces a wide variety of derivatives possessing differing lipid solubilities and rates of hydrolysis to the parent aminoalcohol.

Many biologically active organic compounds containing silicon have been reported and the subject has recently been reviewed (Voronkov & Lukevics, 1969; Garson & Kirchner, 1971). However, there have been only few reports of *O*- and *N*- silyl groups used to modify the metabolic and pharmacokinetic properties of conventional drug molecules (e.g. Chang & Jain, 1966; Upjohn Co., 1968).

This paper describes the synthesis of derivatives of the aminoalcohols methylephedrine, ephedrine and norephedrine, in which various trialkylsilyl groups are attached to the hydroxyl function of the molecule. Measurements of hydrolysis rates and partition coefficients are used to demonstrate the potential use of such trialkylsilyl moieties as functional blocking groups which could be used to modify the pharmacokinetic parameters of drugs.

MATERIALS AND METHODS

Materials

(−)-Methylephedrine hydrochloride and (−)-ephedrine hydrochloride (Koch-Light) and (−)-norephedrine hydrochloride (Ralph Emanuel Ltd.) were recrystallized from hot ethanol before use.

Trimethylchlorosilane was obtained from May and Baker Ltd., triethylchlorosilane and tri-n-propylchlorosilane from Pierce Chemical Company. Other chlorosilanes were synthesized by Dr. G. Davison and were a gift from Dr. K. Thrower, Upjohn Ltd., Crawley, Sussex.

Synthesis of silyl derivatives

Aminoalcohol hydrochloride (0·01 mol), chlorosilane (0·02 mol) and pyridine (30 ml) were heated at 80° under reflux for 1–8 h; strict precautions were taken to avoid access of moisture to the reaction mixture. When the aminoalcohol hydrochloride had dissolved, 2 μl samples of the reaction mixture were withdrawn at different time intervals and examined for unchanged substrate by gas-liquid chromatography (g.l.c.).

When derivatization was complete, the reaction mixture was cooled to room temperature and evaporated to dryness at 50° under reduced pressure. The solid residue was washed with n-hexane (30 ml) to remove excess chlorosilane and pyridine, and dissolved in dry chloroform (10 ml). Diethylether (sodium dried) was added to the

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solution to precipitate pyridine hydrochloride and any unreacted aminoalcohol hydrochloride; the solution was left to stand at 4° for 1 h and filtered. The filtrate was evaporated to low volume (10 ml) and dry n-hexane was added until a precipitate began to form. The solution was left at 4° overnight. Crystals of the silyl derivative of aminoalcohol hydrochloride formed and were removed by filtration. The product was recrystallized from chloroform, ether and hexane by repetition of the above until no unreacted aminoalcohol remained.

Gas-liquid chromatography

A Perkin-Elmer F11 chromatograph with flame ionization detector was used.

For silyl derivatives: the aqueous solution of silyl compound (1 ml) and internal marker solution (1 ml of solution of diphenylamine in distilled water, 0·1 μ mol ml^{-1}) were adjusted to pH 5·8–6·1 by addition of phosphate-citrate buffer (1 ml) and extracted with 4 × 2·5 ml redistilled diethylether. The combined ethereal extracts were concentrated to *ca* 50 μl and 2–5 μl were analysed by g.l.c. Conditions were: 2m, $\frac{1}{4}$ in. o.d. glass column packed with 3% OV–17 on Chromosorb G (acid washed, DMDCS treated, 80–100 mesh): N_2 pressure 15 p.s.i., H_2 pressure 20 p.s.i. and air pressure 20 p.s.i. Oven temperature 175, 180 or 185° (depending on compound being measured); injection block temperature 100° higher than oven temperature.

For aminoalcohols: the aqueous solution remaining after extraction of silyl compounds was analysed for methylephedrine, ephedrine and norephedrine as previously described (Beckett, Gorrod & Taylor, 1972). The chromatographic properties of the silyl derivatives and the aminoalcohols are recorded in Table 1.

Hydrolysis constants of silyl derivatives

McIlvaine's phosphate-citrate buffer (pH 4·0 or 7·4: 8 ml), in a 100 ml conical flask fitted with ground glass stopper, was maintained in a water bath at 37°. Silylephedrine hydrochloride (1 ml) in distilled water (1·0 μ mol ml^{-1}) was added to the flask, the contents mixed rapidly and an aliquot (1 ml) removed immediately. Further aliquots were removed at predetermined time intervals, the contents of the flask being continually agitated. The aliquots were assayed immediately for silyl compound and parent aminoalcohol by the methods described above.

Apparent partition coefficients of silyl derivatives

The apparatus used was as described by Beckett & Moffat, (1969). The aqueous phase consisted of phosphate-citrate buffer pH 6·0 or 7·4 (9 ml) and 1 ml of solution of silyl derivative in distilled water (2·5 or 5·0 μ mol ml^{-1}). n-Heptane (5 ml) was employed as the organic phase.

For each compound, determinations were carried out in triplicate at 0·1 and 0·2 μ mol ml^{-1} with controls containing no organic phase at each concentration.

The contents of the tubes were agitated by rocking through 90° ten times per minute. After 4 h the two phases were centrifuged, separated and aliquots (1 ml) of the aqueous phases analysed for silyl derivative and parent aminoalcohols by g.l.c. as previously described.

Footnote on nomenclature: compounds originating from methylephedrine, ephedrine and norephedrine and comprising a trialkylsilyl moiety attached to the hydroxyl group are generally referred to as 'silyl derivatives' of each particular aminoalcohol. Specific derivatives are represented, for example as DPrMS methylephedrine, indicating the derivative of methylephedrine carrying a di n-propylmethylsilyl group attached to the –OH function of the aminoalcohol.

RESULTS AND DISCUSSION

Synthesis

The method of synthesis described gave 95–100% conversion of aminoalcohol to silyl derivative. After purification the silyl derivatives were obtained as white, crystalline compounds, highly soluble in distilled water and in phosphate citrate buffer at pH values below about 7 (depending on the alkyl substituents). In addition to those compounds shown in Table 1, for which elemental analyses were obtained, the di-n-butylmethylsilyl and tri-n-butylsilyl derivatives of methylephedrine were also synthesized. These compounds, because of their high lipid-solubility, could only be separated from unchanged aminoalcohol and pyridine hydrochloride and could not be separated from excess silylating agent in the manner described for the other compounds and they were therefore used as the unrecrystallized substance.

Hydrolysis

The silyl derivatives underwent pH-dependent hydrolysis in solution; at 37° hydrolysis at pH 1 was extremely fast and the rate immeasurable by the techniques employed, whereas hydrolysis at pH 7·4 was relatively very slow. Measurement of hydrolysis rate was carried out at a concentration of 0·1 μ mol ml^{-1} at pH 4·0 and pH 7·4; rate constants are shown in Table 1. The range of hydrolysis rates obtainable by variation of the silyl group is illustrated in Fig. 1.

Rate constants were obtained from the slope of the plots of log (concentration of silyl compound) against time and log [(initial concentration of silyl-compound)—(concentration of parent aminoalcohol)] against time. Slope of the line of best fit was determined by regression analysis using the method of least squares. A typical plot is shown in Fig. 2. Agreement between rate constants derived from rate of disappearance of silyl compound and those from rate of appearance of parent aminoalcohol was good (better than ±5%); reproducibility of repeat determinations was also better than ±5%.

For the silyl derivatives of methylephedrine, the order of hydrolysis rate constants at pH 4·0 was:

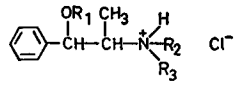
$$\begin{array}{ccccc} \text{TMS} & > & \text{PrDMS} & \geqslant & \text{EtDMS} > \text{BuDMS} \\ & & \vee & & \vee \quad \vee \\ & & \text{DPrMS} & \geqslant & \text{DEtMS} > \text{DBuMS} \\ & & \vee & & \vee \quad \vee \\ & & \text{TPrS} & > & \text{TEtS} > \text{TBuS} \end{array}$$

Hydrolysis of the TPrS derivative of methylephedrine was significantly ($0{\cdot}0005 > P$) faster than for the TEtS derivative; this does not follow the general trend of reduction in hydrolysis rate with increase in size or number of substituent alkyl groups. Hydrolysis constants of PrDMS methylephedrine and DPrMS methylephedrine, however, were very close to those of the corresponding ethyl derivatives, i.e. EtDMS and DEtMS methylephedrine respectively. A similar trend was seen in the hydrolysis constants measured at pH 7·4, although data for some of the more lipophilic members of the series are missing because of the relative insolubility of the compounds in phosphate-citrate buffer at this pH.

In contrast, Akerman (1956), measured the rate of base- and acid-catalysed hydrolysis

Table 1. *Structural formulae of compounds; first order rate constants for the hydrolysis of silyl derivatives in solution at pH 4·0 and pH 7·4; initial concentration (0·1 μmol ml^{-1}) and apparent partition coefficients of aminoalcohols and their silyl derivatives (n-heptane–water, pH 6·0).* (Elemental analyses were within the usual limits for CHO).

General structure



$R_1 = -Si(R')(R'')(R)$ Silyl substituents of norephedrine, ephedrine and methylephedrine hydrochlorides

	Parent Aminoalcohol	Substituents on silyl function R′	R″	R	G.l.c. analysis Column	temp. (°C)	Retn time (min)	Hydrolysis constant, k (μmol min^{-1}) pH 4·0	pH 7·4	Partition coefficient at pH 6·0	πp	π p(-CH_2-)
		(R_1=H; R_2=R_3=Me)										
	Methylephedrine HCl	—	—	—	A	125	8·6	ND	ND	*0·22 × 10^{-2}	ND	ND
TMS	,,	Me	Me	Me	B	155	4·3	0·21	0·66 × 10^{-2}	12·6	ND	ND
EtDMS	,,	Et	Me	Me	B	175	3·7	0·68 × 10^{-1}	0·20 × 10^{-2}	37·3	0·5	0·50
PrDMS	,,	n-Pr	Me	Me	B	175	4·9	0·72 × 10^{-1}	0·23 × 10^{-2}	145	1·1	0·55
BuDMS	,,	n-Bu	Me	Me	B	180	5·8	0·54 × 10^{-1}	0·13 × 10^{-2}	480	1·6	0·53
DEtMS	,,	Et	Et	Me	ND	ND	ND	0·29 × 10^{-1}	ND	ND	ND	ND
DPrMS	,,	n-Pr	n-Pr	Me	B	180	7·6	0·31 × 10^{-1}	0·58 × 10^{-3}	1415	2·1	0·53
DBuMS	,,	n-Bu	n-Bu	Me	ND	ND	ND	0·15 × 10^{-1}	ND	ND	ND	ND
TEtS	,,	Et	Et	Et	B	180	7·6	0·90 × 10^{-2}	0·15 × 10^{-3}	480	1·6	0·53
TPrS	,,	n-Pr	n-Pr	n-Pr	B	185	10·4	0·11 × 10^{-1}	ND	5050	2·7	0·45
TBuS	,,	n-Bu	n-Bu	n-Bu	ND	ND	ND	0·36 × 10^{-2}	ND	ND	ND	ND
											Mean=0·50 ± 0·04	
		(R_1=R_2=H; R_3=Me)										
	Ephedrine HCl	—	—	—	A	125	11·0	ND	ND	*0·78 × 10^{-4}		
PrDMS	,,	n-Pr	Me	Me	B	175	4·8	0·79 × 10^{-1}	0·94 × 10^{-3}	5·2		
TEtS	,,	Et	Et	Et	B	180	7·6	0·89 × 10^{-2}	0·11 × 10^{-3}	26·3		
		(R_1=R_2=R_3=H)										
	Norephedrine HCl	—	—	—	A	125	17·9	ND	ND	*0·8 × 10^{-5}		
PrDMS	,,	n-Pr	Me	Me	B	175	4·5	0·14	0·17 × 10^{-2}	2·5		
TEtS	,,	Et	Et	Et	B	180	7·5	0·18 × 10^{-1}	0·16 × 10^{-3}	11·2	..	

ND not determined.
G.l.c. columns: A: 2% Carbowax 20M/5% KOH on Chromosorb G. B: 3% OV-17 on Chromosorb G. See under Materials and Methods.
* Calculated from values of true partition coefficient (Beckett & others, 1972).

of phenoxysilanes in ethanol–water mixtures and found hydrolysis rate to decrease strictly with increasing size of the alkyl substituents, i.e.

$$TMS \gg TEtS > TPrS > TBuS > TAmS$$

Hydrolysis constants determined for PrDMS and TEtS derivatives of ephedrine are similar to those of the corresponding derivatives of methylephedrine. PrDMS norephedrine and TEtS norephedrine, however, hydrolyse much faster than the corresponding ephedrine derivatives at pH 4·0, but have similar hydrolysis constants at pH 7·4.

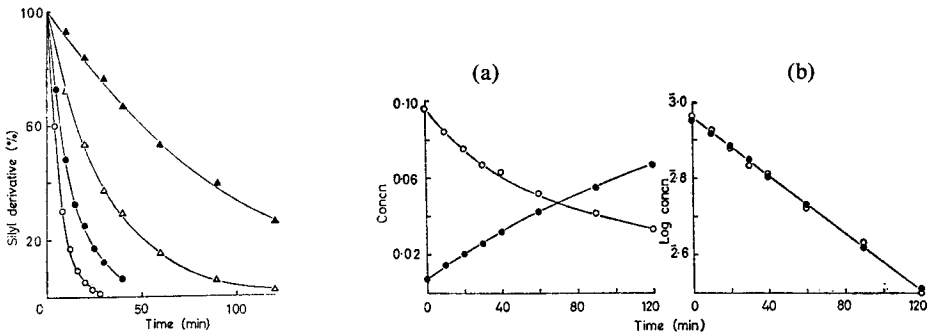


FIG. 1. The hydrolysis of some silyl derivatives of methylephedrine at pH 4·0, 37°. ○ TMS methylephedrine HCl. ● PrDMS methylephedrine HCl. △ DPrMS methylephedrine HCl. ▲ TPrS methylephedrine HCl.

FIG. 2. The hydrolysis of TEtS methylephedrine HCl at pH 4·0, 37°. (a) Concentration against time. ○ TEts methylephedrine. ● Methylephedrine. (b) Log_{10} concentration against time. ○log [TEts methylephedrine]. ● log [Co silyl − Ct methylephedrine].

Apparent partition coefficients

Apparent partition coefficients were measured using the n-heptane–water system; this has previously been used to relate the lipid-solubility of certain organic acids and bases with their buccal absorption in man (Beckett & Moffat, 1969; Beckett & Hossie, 1971).

None of the silyl derivatives examined were water-soluble when fully unionized (i.e. at pH values in the region 10–12); some, the most lipid-soluble, were also partly insoluble at pH 7·4. Phosphate-citrate buffer, pH 6·0, however, was found to be a convenient aqueous phase in which all the derivatives were soluble. Use of lower pH values, while lowering the measured partition coefficient, would have caused significant hydrolysis of the silyl derivative during the course of partition coefficient determination.

Partition coefficients (P) were calculated according to the equations:

$$P = \frac{\text{(Initial} - \text{Final) concentration in aqueous phase}}{\text{Final concentration in aqueous phase}} \quad .. \quad .. \quad .. \quad (1)$$

$$\text{and } P = \sqrt{\frac{\text{(Initial} - \text{Final) concentration in aqueous phase}}{\text{Final concentration in aqueous phase}}} \quad .. \quad .. \quad .. \quad (2)$$

Equation 2 assumes that dimerization of molecules occurs in the organic phase. Partition coefficient values for each compound at two different initial concentrations in the aqueous phase were determined using both equations. For each compound, best agreement between values determined at the two concentrations was obtained

when no dimerization in the organic phase was assumed. Apparent partition coefficient values (calculated from eqn 1) for silyl derivatives of methylephedrine, ephedrine and norephedrine are shown in Table 1; the values shown are the mean of determinations made using initial concentrations of 0·1 and 0·2 μmol ml^{-1} in the aqueous phase. The value obtained for TPrS methylephedrine is approximate due to the extremely low concentration present in the aqueous phase at equilibrium.

Values for the apparent partition coefficients of methylephedrine, ephedrine and norephedrine at pH 6·0 ($P_{6\cdot0}$) were calculated from values of absolute partition coefficient measured under alkaline conditions (Beckett & others, 1972).

The relation seen between lipid solubility of the silyl derivatives of methylephedrine and the substituent alkyl groups on the silicon atom when a plot of log $P_{6\cdot0}$ against number of methylene groups on the silicon atom is made, it is linear up to and including DPrMS methylephedrine, but the log $P_{6\cdot0}$ value for TPrS methylephedrine is somewhat lower than the expected value; this is probably due to inaccuracy in the determination for this derivative.

The effect on the partition coefficient of the addition of each individual methylene ($-CH_2-$) unit to the silicon atom was assessed by calculating the values of the substituent constants πp and πp($-CH_2-$), where πp = (log $P_{6\cdot0}$ of silyl derivative)—(log $P_{6\cdot0}$ of TMS methylephedrine), and $\pi p(-CH_2-) = \frac{\pi p,}{(n-3)}$ where n = total number of methylene units on the silicon atom. πp($-CH_2-$) is then a measure of the effect on partition coefficient of the addition of each successive methylene unit (in excess of trimethylsilyl) to the silyl group (see Table 1). The mean value of πp($-CH_2-$) for the seven silyl derivatives of methylephedrine studied was 0·50 (standard deviation 0·04).

In conclusion, we have shown that attachment of a trialkylsilyl moiety to the hydroxyl function of an aminoalcohol hydrochloride, such as the three 'ephedrines' used in this study, can afford a series of derivatives by variation of the alkyl substituent on the silicon atom. The derivatives described in this study are water-soluble due to the presence of the amine hydrochloride function.

The partition coefficients of the derivatives, and rate of hydrolysis to the parent aminoalcohol, can be controlled by variation of the alkyl substituents on the silicon atom. It is likely that the enhanced lipid solubility conferred on a drug molecule would affect transfer across lipid membranes *in vivo* and, once in the biophase, the silyl derivative would hydrolyse (either chemically or metabolically) to regenerate the parent drug molecule. Control of these factors in this way may allow control of the pharmacokinetic parameters of a drug i.e. the factors controlling absorption, distribution and elimination.

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