Synthesis and Properties of a Series of Sterically Hindered Guanidine Bases [1]

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By the reaction of Vilsmeier salts, derived from tetra-alkylureas or from tetra-alkylthioureas, with primary aliphatic amines, a series of sterically hindered penta-alkyl guanidines has been prepared. 2-t-Butyl-1',1',3'',3''-tetramethylguanidine and pentaisopropylguanidine combine ease of preparation with a range of resistance to alkylating agents. Preliminary experiments indicate that these inexpensive bases will be useful in organic synthesis.

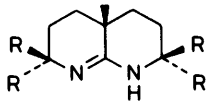
STERICALLY hindered tertiary amines are widely used in organic synthesis as proton acceptors.[2] They show relatively low nucleophilicity, a property seen to a marked degree in 2,6-di-t-butylpyridine and its congeners.[3]

The stronger amidine bases DBN (1,5-diazabicyclo-[4.3.0]non-5-ene) and DBU (1,8-diazabicyclo[5.4.0]-undec-7-ene) are of proven synthetic utility, but they are easily alkylated and are not inexpensive.[4]

Derivatives of 1,8-diaminonaphthalene give very strong non-nucleophilic bases with, in appropriate examples, pK_a values of >16.[5] However, proton transfer may be slow and such compounds may never be cheap.

Hindered amidines are strong bases and show low nucleophilic character. Two compounds of interest are (1a) and (1b).[6]

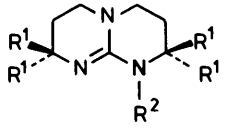
Strong guanidine bases have long been known,[7] but there is little work on the modification of their nucleophilic character by steric hindrance. Exceptions to this are the interesting compounds (2a—c).[8]



(1)

a; R = H

b; R = Me



(2)

a; R^1 = Me, R^2 = H

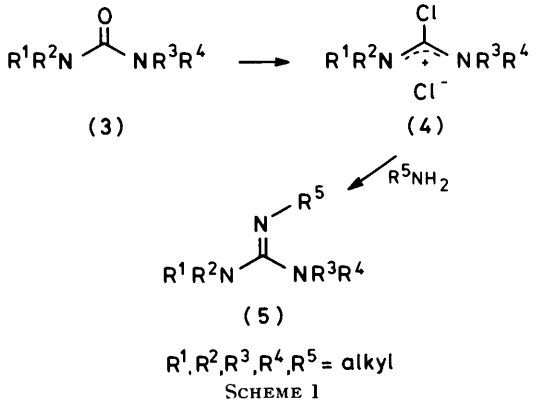
b; R^1 = H, R^2 = H

c; R^1 = H, R^2 = Me

We considered that it should be possible to synthesise, easily and inexpensively, penta-alkylguanidines (5) with all three nitrogens too hindered to be alkylated. In Scheme 1, a Vilsmeier salt is formed from a urea and is then treated with an excess of a primary amine to give compounds (5). In fact, the guanidine (6) has previously been reported,[9] but was neither characterised (except by its n.m.r. spectrum) nor used as a base.

Guanidines (6), (7), and (8), of increasing steric hindrance, were prepared in good yield according to Scheme 1 through the sequence (3) ⟶ (4) ⟶ (5).

Our attempts to prepare even more hindered compounds by this route were thwarted, however, by the reluctance of *N,N,N',N'*-tetraisopropylurea (9) to provide the desired Vilsmeier salt (10). The trend towards decreasing reactivity of tetra-alkylureas (3) with phosgene, due to increasing steric hindrance, was noticeable during the preparation of compounds (6), (7), and (8),



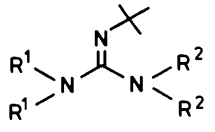
(3) (4) (5)

R^1, R^2, R^3, R^4, R^5 = alkyl

SCHEME 1

but was even more clearly demonstrated by the urea (9), which gave only a trace of compound (10) upon treatment with an excess of phosgene for three months at room temperature.

To overcome this difficulty we turned our attention to *N,N,N',N'*-tetraisopropylthiourea (11), prepared by



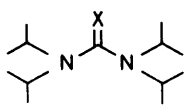
(6) $R^1 = R^2$ = Me

(7) $R^1 = R^2$ = Et

(8) R^1 = Pri, R^2 = Et

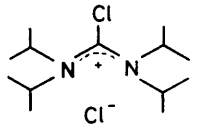
the reaction of di-isopropylamine with thiophosgene. As anticipated, on the grounds of the greater nucleophilicity of thioureas in comparison with the corresponding ureas,[10] compound (11) reacted rapidly to give the very hygroscopic Vilsmeier salt (10) which, when treated with either ammonia or the appropriate primary amine, afforded the corresponding guanidine (12), (13), or (14) in good overall yield from the thiourea (11). The

salt (10) proved to be very resistant to guanidine formation with t-butylamine and even the most favourable conditions (*i.e.* reflux for three weeks in acetonitrile) gave only a low yield of compound (15), which is the most hindered guanidine yet synthesised.



(9) X = O

(11) X = S



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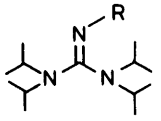


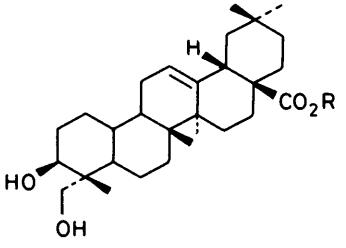
(12) R = H (14) R = Pr^i

(13) R = Et (15) R = Bu^t

The comparative rates of alkylation of these bases by methyl iodide and by benzyl bromide were reported in our preliminary communication.[1] The base (6) alkylates surprisingly easily, but nevertheless catalyses other reactions even more quickly (see below). Pentaisopropylguanidine (14) is alkylated very slowly compared with all tertiary amines we tested and, since it is easy to synthesise, it is suitable for proton attack without any complications arising. DBN we found, in comparison, was rapidly alkylated under the above conditions.

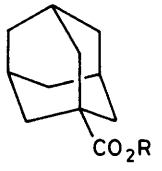
It has been shown that the salt of a carboxylic acid may be alkylated with an alkyl halide in the presence of DBU to give the appropriate ester.[11] Our investigations showed that the guanidine (6) is particularly suitable for this transformation, even in the case of severely hindered carboxylic acids. Thus hederagenin (16) was converted into its methyl ester (17) in 88% yield by treating it with methyl iodide in the presence of the guanidine (6) in *N*,*N*-dimethylformamide. Likewise, alkylation of the salt of adamantane-1-carboxylic acid (18) and compound (6) with isopropyl iodide furnished the isopropyl ester (19) in 91% yield.

Xanthates have been shown to be important intermediates in the deoxygenation of alcohols and may be prepared, in certain cases, by treatment of the requisite alcohol with carbon disulphide and DBN, followed by the addition of methyl iodide.[12] We decided, therefore, to test the suitability of guanidine (6) in this context. However, when compound (6) was treated with carbon disulphide, an exothermic reaction led very rapidly to the formation of *N*,*N*,*N*′,*N*′-tetramethylthiourea (20). Our mechanistic interpretation of this result (Scheme 2) was corroborated by trapping the co-product of the reaction, t-butyl isothiocyanate (21), with isopropylamine to give *N*-t-butyl-*N*′-isopropylthiourea (22).



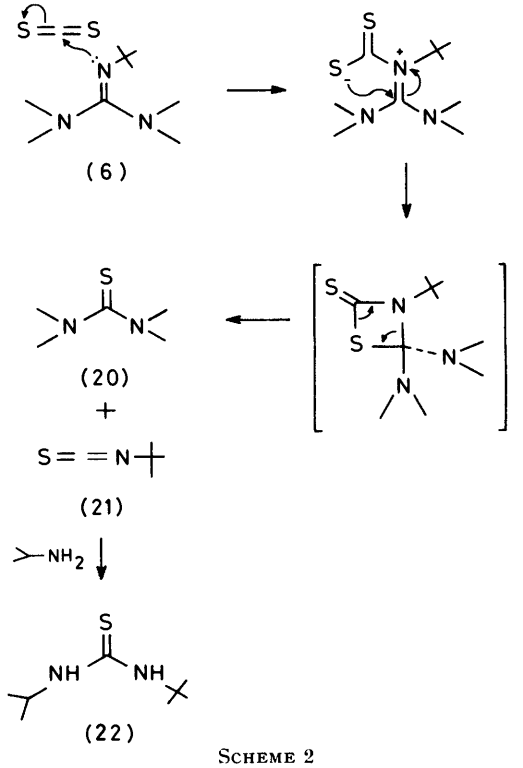
(16) R = H

(17) R = Me



(18) R = H

(19) R = Pr^i



(6)

(20)

+

S=C=N+

(21)

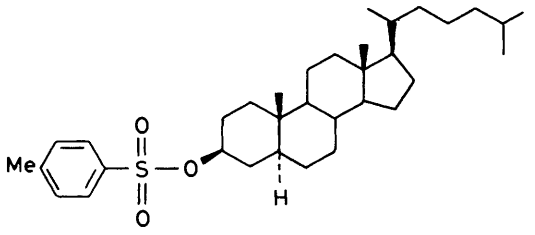
NH$_2$

(22)

SCHEME 2

The amidine bases DBN and DBU have been used extensively in dehydrohalogenation reactions and in the elimination of sulphonic acids from the corresponding esters.[4] When cholestan-3β-yl toluene-*p*-sulphonate (23) was heated at 120 °C for 24 h with compound (6), elimination of toluene-*p*-sulphonic acid occurred to give a mixture of cholest-2-ene (24) and cholest-3-ene (25) in 51% yield. The moderate yield in this reaction is probably a result of competing alkylation of the base since, under similar conditions, the more hindered guanidines (8) and (14) gave the same mixtures of alkenes (24) and (25) in 79 and 85% yield, respectively. Our results compare favourably with the published method [13] for this transformation whereby heating compound (23) at 170 °C for 6 h with collidine gave a 63% yield of the mixture of alkenes (24) and (25). The same reaction performed using DBN as base gave an inferior yield (31%) but at the lower temperature of 80—90 °C. This may reflect a problem of a slow proton-transfer rate,

already encountered with several hindered bases, and extensively studied in connection with the naphthalenediamine bases.[5]



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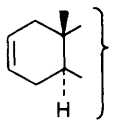

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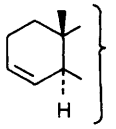

(25)

The alkylation [14] of ethyl 3-oxobutanoate (26) in ether solution with the guanidine (6) (1 equiv.) and methyl iodide (2 equiv.) proceeded rapidly at room temperature to give a good yield (80%) of the monomethylated compound (27), together with a minor quantity (13%) of the dimethylated material (28) (g.l.c. and ^{1}H n.m.r. spectroscopy [15]). The corresponding *O*-methylated compound (29) could not be detected by g.l.c. or n.m.r. spectroscopy. Further treatment of the product with guanidine (6) and methyl iodide (excess) in benzene gave the dimethylated compound (28) (91%) together with some monomethylated material (27) (9%) (g.l.c. and ^{1}H n.m.r. spectroscopy).

It is interesting to consider the effect of steric hindrance on the basic strength of these guanidines. The base (6) showed a pK_a value of *ca.* 14 in 50% aqueous ethanol. Tetramethylguanidine, determined under the same conditions, showed a pK_a value of 13.3, which is in reasonable agreement with that (13.6) recorded in water.[16] In repeating the determination in water we found also pK_a 13.6. DBN in 50% aqueous ethanol showed a pK_a value of *ca.* 13.5. Clearly, the strength of base (6) is not reduced by the presence of the t-butyl group.

In conclusion we have synthesized a number of sterically hindered bases which have been shown to have a variety of properties of potential value in organic synthesis. In addition these compounds are, with the exception of compound (15), readily available from inexpensive precursors.

$MeCOCR^1R^2CO_2Et$

(26) $R^1 = R^2 = H$

(27) $R^1 = Me, R^2 = H$

(28) $R^1 = R^2 = Me$

$MeC(OMe)=CHCO_2Et$

(29)

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 141 polarimeter. I.r. spectra were recorded on a Perkin-Elmer 297 spectrometer. ^{1}H N.m.r. spectra were recorded on Varian T60 or EM 360L (60 MHz) instruments or on a Brucker 80 MHz instrument. Mass spectra were recorded on either an A.E.I. MS-9 or an A.E.I. MS-50 spectrometer.

T.l.c. was performed on Schleicher and Schüll plastic-backed silica gel plates (F1500 S254); the plates were initially examined under u.v. light (254 and 366 nm) then developed with either iodine vapour, an aqueous potassium permanganate spray, or an acidic solution of ammonium molybdate. Column chromatography was effected, under low pressure, using Merck Kieselgel (Type 60) (eluant given in parentheses). Evaporations were carried out at below 40 °C using a Büchi rotary evaporator.

Acetonitrile was pre-dried with Linde 4 Å molecular sieves, then refluxed for 0.5 h with 0.5% phosphorus pentaoxide, followed by distillation.

Diethylamine was dried over potassium hydroxide and distilled. t-Butylamine, di-isopropylamine, and isopropylamine were refluxed with sodium then distilled.

All solvents were dried and distilled; starting materials were purified. Extracts were dried over anhydrous sodium sulphate. Ether refers to diethyl ether.

2-*t*-*Butyl*-1,1,3,3-*tetramethylguanidine* (6).—To a stirred solution of phosgene (8.29 g, 0.084 mol) in dry toluene (25 ml) at 0 °C was added dropwise, dried, distilled *N,N,N′,N′*-tetramethylurea (5.00 g, 0.043 mol) in dry benzene (20 ml). The product was left at room temperature for 1 h and then the solvents and excess of phosgene were evaporated off. The crystalline hygroscopic residue was dissolved in acetonitrile (10 ml) and to this solution, cooled to 0 °C, was added dropwise with stirring, t-butylamine (15 ml, 0.143 mol). The mixture was refluxed for 2 h, cooled, and the solvents were evaporated off. The residue was triturated with ether (4 × 50 ml) and mixed cautiously with 25% aqueous sodium hydroxide (40 ml). The product was extracted with ether (2 × 125 ml) and the extract was dried. The solution was filtered and evaporated to give a light yellow oil. Distillation under reduced pressure gave the guanidine (6) as a liquid which was stored under nitrogen (6.25 g, 85%), b.p.$_{20}$ 80—82 °C [b.p.$_{760\ mmHg}$ 178—183 °C]; $\nu_{max.}$ (film) 1 620 cm^{-1} (C=N); δ ($CDCl_3$) 1.22 (9 H, s, But) and 2.67 (12 H, s, 4 × Me); *m/z* 171 (M^+). Kessler, Leibfritz, the n.m.r. and Burk [9] did not quote any data for this compound except (identical with ours).

2-*t*-*Butyl*-1,1,3,3-*tetraethylguanidine* (7).—To *N,N,N′,N′*-tetraethylurea (12.0 g, 0.07 mol) was added phosgene (39.50 g, 0.40 mol) in ether (100 ml) and the mixture was kept at room temperature for 24 h. The ether and excess of phosgene were evaporated off to give an orange gum which was dissolved in acetonitrile (10 ml). To this cooled solution (ice-bath) was added, cautiously, dry t-butylamine (30 ml, 0.28 mol) and the mixture was left for 15 h at room temperature. The solvents were evaporated off and the residue was carefully triturated with ether to give a white crystalline solid. The solid was mixed with 25% aqueous potassium hydroxide (100 ml) and extracted with ether. The extract was dried, filtered, and evaporated to give a pale yellow oil, distillation of which under reduced pressure gave the *title compound* as a liquid (7.64 g, 48%), b.p. 60—62 °C

at 0.05 mmHg; $\nu_{max.}$ (neat) 2 975, 2 940, and 2 875 (C–H stretch) and 1 620 cm^{-1} (C=N); δ ($CDCl_3$) 1.00 (12 H, t, *J* 7 Hz, 4 × CH_2Me), 1.21 (9 H, s, Bu^t), and 3.00 (8 H, q, *J* 7 Hz, 4 × CH_2Me); *m/z* 227 (M^+) (Found: C, 68.7; H, 12.8; N, 18.7. $C_{13}H_{29}N_3$ requires C, 68.66; H, 12.85; N, 18.48%).

2-*t-Butyl*-1,1-*diethyl*-3,3-*di-isopropylguanidine* (8).—To a solution of *N,N*-diethyl-*N'*,*N'*-di-isopropylurea (11.305 g, 0.05 mol) in dry ether (40 ml) was added a solution of phosgene (20 ml, 0.28 mol) in ether (50 ml). After 9 d at room temperature evaporation of the solvent and excess of phosgene gave a white, hydroscopic solid which was dissolved in acetonitrile (20 ml); dried, distilled t-butylamine (40 ml) was then added and the mixture was refluxed for 72 h. On cooling the solvents were evaporated off and the residue was triturated with ether. The product was mixed with excess of 25% aqueous potassium hydroxide and extracted with ether. The extract was washed with brine and was then dried. Filtration and evaporation gave a light yellow liquid. After drying over potassium hydroxide, distillation under reduced pressure gave the *title compound* (8) as a liquid (8.32 g, 62%), which was stored under nitrogen at 0—5 °C, and had b.p.$_{0.1\ mmHg}$ 74—77 °C; $\nu_{max.}$ (neat) 1 614 cm^{-1} (C=N); δ ($CDCl_3$) 1.03 (6 H, t, *J* 7 Hz, 2 × CH_2Me), 1.20 (12 H, d, *J* 7 Hz, 2 × $CHMe_2$), 1.2 3(9 H, s, Bu^t), 2.97 (4 H, q, *J* 7 Hz, 2 × CH_2Me), and 3.35 (2 H, septet, *J* 7 Hz, 2 × $CHMe_2$); *m/z* 255 (M^+) (Found: C, 70.7; H, 13.0; N, 16.45. $C_{15}H_{33}N_3$ requires C, 70.53; H, 13.02; N, 16.45%).

N,N-*Diethyl*-N',N'-*di-isopropylurea*.—To a stirred solution of phosgene (3.46 g, 3.49 mmol) in ether (30 ml) at −78 °C, dried, distilled di-isopropylamine (12.5 ml, 8.9 mmol) was added dropwise. The mixture was warmed to room temperature and then left for 0.5 h. The product was filtered off and the residue was washed carefully with ether. The combined filtrate and washings were evaporated to give a white solid which was mixed with excess of dry diethylamine (50 ml, 0.48 mol) in a flask equipped with a reflux condenser. After 3 h at room temperature the excess of amine was evaporated off and the product was partitioned between water and ethyl acetate. The organic phase was washed successively with 1M aqueous hydrochloric acid, water, saturated sodium hydrogen carbonate, and brine. It was then dried, filtered and evaporated to give a liquid, distillation of which under reduced pressure gave the *title compound* as a liquid (4.91 g, 70%), b.p.$_{0.03\ mmHg}$ 54—57 °C; $\nu_{max.}$ (neat) 1 645 cm^{-1} (C=O); δ ($CDCl_3$) 1.05 (6 H, t, *J* 7Hz, 2 × CH_2Me), 1.23 (12 H, d, *J* 7 Hz, 2 × $CHMe_2$). 3.02 (4 H, q, *J* 7 Hz, 2 × CH_2Me), and 3.30 (2 H, septet, *J* 7 Hz, 2 × $CHMe_2$); *m/z* 200 (M^+), 185 ($M^+ - CH_3$), and 157 ($M^+ - C_3H_7$) (Found: C, 65.95; H, 12.2; N, 14.1. $C_{11}H_{24}N_2O$ requires C, 65.95; H, 12.08; N, 13.99%).

N,N,N',N'-*Tetraisopropylurea* (9).—To a stirred solution of phosgene (20 g, 0.2 mol) in ether (50 ml) at 0 °C, dried, distilled di-isopropylamine (60 ml) was added dropwise. After 1 h at room temperature the mixture was filtered and the residue was washed with dry ether. The combined filtrate and washings were evaporated to give a white solid. This material was mixed with dried, distilled di-isopropylamine (100 ml) and the mixture was refluxed for 14 d. The product was evaporated to dryness and the residue was partitioned between 1M aqueous hydrochloric acid and ether. The aqueous phase was back-extracted with ether and the combined organic extracts were washed successively with water, saturated aqueous sodium hydrogen carbonate, water, and brine. After drying and filtration, evaporation gave a light yellow liquid, distillation of which under reduced pressure gave the *title compound* (9) as a liquid (27.0 g, 58%), b.p.$_{0.1\ mmHg}$ 85—90 °C; $\nu_{max.}$ ($CHCl_3$) 1 630 cm^{-1} (C=O); δ ($CDCl_3$) 1.20 (24 H, d, *J* 7 Hz, 4 × $CHMe_2$), and 3.52 (4 H, septet, *J* 7 Hz, 4 × $CHMe_2$) (Found: C, 68.3; H, 12.5; N, 12.35. $C_{13}H_{29}N_2O$ requires C, 68.37; H, 12.36; N, 12.27%).

N,N,N',N'-*Tetraisopropylthiourea* (11).—To dried, distilled di-isopropylamine (100 ml, 0.71 mol) cooled to −50 °C was slowly added thiophosgene (10 ml, 0.1 mol). The mixture was warmed to 0 °C and after 15 min a further quantity of di-isopropylamine (50 ml, 0.35 mol) was added and the mixture was refluxed for 8 h. After cooling, the excess of di-isopropylamine was evaporated off and the residue was partitioned between ether and 1M-aqueous hydrochloric acid. The organic phase was washed with water, saturated aqueous sodium hydrogen carbonate, water, and brine. The solution was dried, filtered, and evaporated to give a dark red liquid which was purified by low-pressure column chromatography to give the *title thiourea* (11) (14.13 g, 44%) as a pale yellow liquid, b.p.$_{0.3\ mmHg}$ 100 °C; $\nu_{max.}$ 1 220 and 1 300 cm^{-1}; δ ($CDCl_3$) 1.28 (24 H, d, *J* 7 Hz, 4 × $CHMe_2$ and 4.08 (4 H, septet, *J* 7 Hz, 4 × $CHMe_2$); *m/z* 244 (M^+) and 201 ($M^+ - C_3H_7$) (Found: C, 64.0; H, 11.65; N, 11.65. $C_{12}H_{28}N_2S$ requires C, 63.88; H, 11.55; N, 11.46%).

1,1,3,3-*Tetraisopropylguanidine* (12).—To dried, distilled *N,N,N',N'*-tetraisopropylthiourea (11) (1.078 g, 4.42 mmol) was added a solution of phosgene (2 ml, 0.28 mmol) in ether (10 ml). After 2 h at room temperature evaporation of the solvent and excess of phosgene gave an off-white solid. Through a solution of this solid in acetonitrile (2 ml) at 0 °C was passed excess of ammonia gas. The solvent was then evaporated off and the product was triturated with ether. The product was partitioned between excess of 25% aqueous potassium hydroxide and ether. The organic phase was washed with brine, dried, filtered, and evaporated to give a light brown liquid (0.87 g, 81%). Bulb-to-bulb distillation under reduced pressure gave the *title compound* (12) as a liquid; $\nu_{max.}$ (neat) 3 350—3 100 (N–H) and 1 590 cm^{-1} (C=N); δ ($CDCl_3$) 1.20 (24 H, d, *J* 7 Hz, 4 × $CHMe_2$), 3.65 (4 H, septet, *J* 7 Hz, 4 × $CHMe_2$), and 5.55br. (1 H, NH) (addition of D_2O caused the signal at δ 5.55 to disappear); *m/z* 227 (M^+) and 184 ($M^+ - C_3H_7$) (Found: C, 68.55; H, 12.8; N, 18.5. $C_{13}H_{29}N_3$ requires C, 68.66; H, 12.85; N, 18.48%).

2-*Ethyl*-1,1,3,3-*tetraisopropylguanidine* (13).—Similarly, compound (11) (0.963 g, 3.95 mmol) and phosgene (2 ml, 0.028 mol) in ether (10 ml) gave an off-white solid, to a solution of which in acetonitrile (3 ml) at 0 °C was added, dropwise, anhydrous ethylamine (5 ml). After 0.5 h at room temperature the mixture was worked up as for compound (12) to give a light yellow liquid (0.86 g, 85%). Bulb-to-bulb distillation under reduced pressure gave the *title compound* (13) as a liquid; $\nu_{max.}$ (neat) 1 610 cm^{-1} (C=N); δ ($CDCl_3$) 1.10 (3 H, t, *J* 7 Hz, CH_2Me), 1.15 (12 H, d, *J* 7 Hz, 2 × $CHMe_2$), 1.25 (12 H, d, *J* 7 Hz, 2 × $CHMe_2$), 3.18 (2 H, q, *J* 7 Hz, CH_2Me), 3.40 (2 H, septet, *J* 7 Hz, 2 × $CHMe_2$), and 3.76 (2 H, septet, *J* 7 Hz, 2 × $CHMe_2$); *m/z* 255 (M^+) and 212 ($M^+ - C_3H_7$) (Found: C, 70.7; H, 13.15; N, 16.75. $C_9H_{21}N_3$ requires C, 70.63; H, 13.02; N, 16.45%).

1,1,2,3,3-*Pentaisopropylguanidine* (14).—Similarly, compound (11) (14.00 g, 0.057 mol) and phosgene (11.0 g, 0.11 mol) in ether (60 ml) gave, after 1 h, a pale brown, hygroscopic solid. The product was dissolved in acetonitrile

(30 ml) and to this solution, cooled in an ice-bath, was slowly added dried, distilled isopropylamine (45 ml). After being kept overnight at room temperature, identical work-up as before gave a pale orange liquid. The material was dried over potassium hydroxide pellets then distilled under reduced pressure to give the *title compound* (14) (10.61 g, 69%) as a liquid, b.p.$_{0.01\ mmHg}$ 60 °C; $\nu_{max.}$ (neat) 1 605 cm^{-1} (C=N); δ ($CDCl_3$) (80 MHz) 1.05 (6 H, d, *J* 7 Hz, CH*Me*$_2$), 1.14 (12 H, d, *J* 7 Hz, 2 × CH*Me*$_2$), 1.23 (12 H, d, *J* 7 Hz, 2 × CH*Me*$_2$), 3.35 (2 H, septet, *J* 7 Hz, 2 × C*H*Me$_2$), 3.35 (1 H, septet, *J* 7 Hz, C*H*Me$_2$), and 3.78 (2 H, septet, *J* 7 Hz, 2 × C*H*Me$_2$) (the above assignments were confirmed by the appropriate decoupling experiments); *m/z* 269 (M^+) and 226 ($M^+ - C_3H_7$) (Found: C, 71.2; H, 13.1; N, 15.8. $C_{16}H_{35}N_3$ requires C, 71.31; H, 13.09; N, 15.59%). Compound (14) was stored at −20 °C under argon and solidified under these conditions.

2-*t*-*Butyl*-1,1,3,3-*tetraisopropylguanidine* (15).—In an identical manner, compound (11) (2.41 g, 9.9 mmol) and phosgene (5 ml, 0.07 mol) in ether (25 ml) gave an off-white solid which was dissolved in *rigorously* dried, distilled acetonitrile (5 ml) and *rigorously* dried, distilled t-butylamine (20 ml) was added. The mixture was refluxed for 21 days with exclusion of moisture and with occasional addition of t-butylamine to maintain an approximately constant volume. Work-up as above gave a brown oil which was dissolved in ether and the solution was treated with an excess of a solution of hydrogen chloride in ether; the solid precipitate which formed was triturated carefully with ether. The hydrochloride, which was hygroscopic, was treated, as previously described, to regenerate compound (15) as a brown, waxy solid. The product was purified by bulb-to-bulb distillation under reduced pressure to give the *title compound* (15) (1.07 g, 38%) as a pale yellow solid; $\nu_{max.}$ ($CHCl_3$) 1 615 cm^{-1} (C=N); δ ($CDCl_3$) 1.13 and 1.23 (total 33 H, s and d superimposed, 11 % Me) and 3.40 (4 H, septet, *J* 7 Hz, 4 × C*H*Me$_2$); *m/z* 283 (M^+), 240 ($M^+ - C_3H_7$), and 226 ($M^+ - C_4H_9$) (Found: C, 71.75; H, 13.1; N, 14.6. $C_{17}H_{37}N_3$ requires C, 72.02; H, 13.16; N, 14.82%).

Methyl Hederageninate (17).—To a solution of compound (6) (0.199 g, 1.16 mmol) in *N*,*N*-dimethylformamide (3 ml) was added hederagenin (16) (0.41 g, 0.87 mmol). The mixture was warmed until the solid dissolved and was then left to cool to room temperature. Methyl iodide (1 ml, 0.016 mol) was added and after 1 h the excess was removed by evaporation. Addition of water precipitated methyl hederagenate (17). The precipitate was washed carefully with water and dried *in vacuo* (0.371 g, 88%), identical with an authentic specimen.

Isopropyl Adamantane-1-*carboxylate* (19).—To a solution of adamantane-1-carboxylic acid (18) (0.289 g, 1.60 mmol) in benzene (3 ml) was added compound (6) (0.344 g, 2.01 mmol). To this solution was added isopropyl iodide (1 ml, 10.02 mmol) at room temperature. After approximately 5 min a heavy yellow oil separated from the solution. After 0.5 h the solvent and excess of isopropyl iodide were evaporated off to give a yellow oil which was partitioned between ether and 1M aqueous hydrochloric acid. The aqueous phase was back-extracted with ether. The combined extracts were washed successively with water, saturated aqueous sodium hydrogen carbonate, water, 5% aqueous sodium thiosulphate, and brine and were then dried, filtered, and evaporated to give the *ester* (19) as a chromatographically homogeneous oil which crystallised with time (0.32 g, 91%). The product was purified by bulb-to-bulb distillation under reduced pressure, m.p. 29—30 °C; $\nu_{max.}$ ($CDCl_3$) 1 710 cm^{-1} (C=O); δ ($CDCl_3$) 1.18 (6 H, d, *J* 6 Hz, CH*Me*$_2$), 1.5—2.2 (15 H, complex, 6 × CH_2 and 3 × CH), and 4.85 (1 H, septet, *J* 6 Hz, C*H*Me$_2$); *m/z* 222 (M^+) (Found: C, 75.41; H, 10.05. $C_{14}H_{22}O_2$ requires C, 75.63; H, 9.97%).

Reaction of 2-*t*-*Butyl*-1,1,3,3-*tetramethylguanidine* (6) *with Carbon Disulphide*.—(a) To the guanidine (6) (0.787 g, 4.6 mmol) was added excess of carbon disulphide (2 ml) and the solution was left for 0.5 h. The mixture was evaporated under reduced pressure to remove excess of carbon disulphide and was then evaporated to dryness on a high-vacuum pump. The crystalline residue was recrystallised from hexane to give *N*,*N*,*N*′,*N*′-tetramethylthiourea (20) as crystals (0.50 g, 83%), m.p. 71—79 °C.

(b) To the guanidine (6) (1.15 g, 6.73 mmol) was added excess of carbon disulphide (2 ml) and the solution was left for 0.5 h. The mixture was evaporated under reduced pressure to remove excess of carbon disulphide (water bath at 20 °C) and dried, distilled isopropylamine (2 ml) was then added dropwise. After 1.5 h at room temperature excess of isopropylamine was evaporated off to give an off-white crystalline residue. Repeated recrystallisation from ether–hexane gave *N*-t-butyl-*N*′-isopropylthiourea (22) as needles (0.80 g, 68%), m.p. 150—152 °C. The mother-liquor was evaporated to dryness and the residue was purified by column chromatography (ether–hexane 1 : 2) to give *N*,*N*,*N*′,*N*′-tetramethylthiourea (20) (0.65 g, 75%), m.p. 75—77 °C.

Reaction of Cholestan-3β-*yl Toluene*-p-*sulphonate* (23) *with* 2-*t*-*Butyl*-1,1,3,3-*tetramethylguanidine* (6).—Cholestan-3β-yl-toluene-*p*-sulphonate (23) (0.413 g, 0.76 mmol) was heated with the guanidine (6) (2 ml) at 120 °C for 24 h. After cooling, the product was partitioned between ether and excess of 1M-aqueous hydrochloric acid. The organic phase was washed successively with water, saturated aqueous sodium hydrogen carbonate, water, and brine and was then dried, filtered, and evaporated. Column chromatography (ether–hexane 1 : 10) gave a mixture of cholest-2- and -3-enes as a crystalline solid (0.145 g, 51%). Recrystallisation from ethyl acetate–methanol gave needles, m.p. 68—69 °C; $[\alpha]_D$ +61° (*c*, 1 in $CHCl_3$), a mixture.

Reaction of Cholestan-3β-*yl Toluene*-p-*sulphonate* (23) *with* 2-*t*-*Butyl*-1,1-*diethyl*-3,3-*di*-*isopropylguanidine* (8).—Cholestan-3β-yl toluene-*p*-sulphonate (23) (0.269 g, 0.50 mmol) was mixed with the guanidine (8) (1.34 g, 5.25 mmol) and the mixture was heated at 120 °C for 20 h. After cooling, the product was partitioned between excess of 1M-aqueous hydrochloric acid and ether. The organic phase was washed successively with water, saturated aqueous sodium hydrogen carbonate, water, and brine and was then dried, filtered, and evaporated to give an oil. This was purified by column chromatography (ether–hexane 1 : 10) to give a mixture of cholest-2- and -3-enes as a crystalline solid (0.145 g, 79%). Recrystallisation from ethyl acetate–methanol gave long needles, m.p. 68—71 °C (lit.,[17] 67—68 °C); $[\alpha]_D^{20}$ +59° (*c*, 1.1 in $CHCl_3$) (lit.,[17] +62°; *c*, 4.9 in $CHCl_3$).

Reaction between 1,1,2,3,3-*Pentaisopropylguanidine* (14) *and Cholestan*-3β-*yl Toluene* -p-*sulphonate* (23).—The sulphonate (23) (0.422 g, 0.80 mmol) was mixed with the guanidine (14) (0.1 g, 3.71 mmol) and the mixture was heated to 120 °C under nitrogen for 26 h. After cooling, the product was partitioned between ether and excess of 1M aqueous hydrochloric acid. The organic phase was washed successively with water, saturated aqueous sodium hydrogen

carbonate, water, and brine, and was then dried, filtered, and evaporated to give a light brown crystalline solid. Purification by column chromatography (ether–hexane 1 : 10) gave a mixture of cholest-2- and -3-enes as a crystalline solid (0.25 g, 85%). Recrystallisation from ethyl acetate–methanol gave needles, m.p. 68—70 °C; $[\alpha]_D$ +61° (*c*, 1.1 in $CHCl_3$), a mixture.

Methylation of Ethyl 3-*Oxobutanoate* (26) *in the Presence of* 2-*t-Butyl*-1,1,3,3-*tetramethylguanidine* (6).—(a) To a solution of distilled ethyl 3-oxobutanoate (26) (0.197 g, 1.52 mmol) in ether (2 ml) was added a solution of the guanidine (6) (0.265 g, 1.55 mmol) in ether (1 ml). The mixture was cooled to 0 °C and methyl iodide (0.25 ml, 4.0 mmol) was added. After 1 h at room temperature the solvent and excess of methyl iodide were evaporated off and the product was partitioned between 1M aqueous hydrochloric acid and ether. The organic phase was washed with water and then with brine, after which it was dried, filtered, and evaporated to give a very pale yellow liquid (0.20 g), g.l.c. analysis (Girdel column SE/30, 5%, 1.5 m) of which revealed that the product contained ethyl 3-oxobutanoate (26) (7%), ethyl 2-methyl-3-oxobutanoate (27) (80%) and ethyl 2,2-dimethyl-3-oxobutanoate (28) (13%). The constitution of the mixture was confirmed by ^1H n.m.r. spectroscopy.

(b) To a solution of the above product in benzene (2 ml) was added a solution of the guanidine (6) (0.283 g, 1.66 mmol) in ether (1 ml), followed by the dropwise addition of excess of methyl iodide (1 ml). Work-up as before after 0.5 h gave a liquid (0.201 g), g.l.c. analysis (details as above) of which revealed that the product contained ethyl 2-methyl-3-oxobutanoate (27) (9%) and ethyl 2,2-dimethyl-3-oxobutanoate (28) (91%). The constitution of the mixture was confirmed by ^1H n.m.r. spectroscopy.

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