The Synthesis and Properties of a Series of Strong but Hindered Organic Bases

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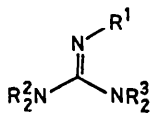
Summary A series of highly hindered N^1,N^2,N^2,N^3,N^3-penta-alkylguanidines has been synthesised from inexpensive starting materials; these strong bases show interesting effects in organic synthesis.

HINDERED organic bases play an important role in organic synthesis.[1] Strong bases of the amidine type are less numerous, but also show valuable synthetic applications.[2] These amidine bases are rather expensive. It seemed to us that it would be interesting to synthesise, from cheap starting materials, a series of guanidine bases even more hindered than the amidine bases used before.

Treatment of the appropriate tetra-alkylureas in benzene or ether at 0 °C to room temperature with phosgene in toluene or in ether gave the corresponding Vilsmeier salts in good yield. Removal of the solvents *in vacuo* and addition of t-butylamine afforded the hindered guanidines (**1**)—(**3**) as colourless liquids.† The most hindered bases (**6**) and (**7**) and compounds (**4**) and (**5**) could not be obtained conveniently from tetra-isopropylurea. They, however, were prepared from the corresponding more reactive thiourea *via* the Vilsmeier salt. For the base (**6**) the t-butylamine was introduced by heating under reflux for 3 weeks using an excess of the amine. We believe that compound (**6**), which was the only base obtained in low yield, is the most hindered guanidine yet prepared. Compound (**7**), which has comparable hindrance to (**6**), is more easily prepared using isopropylamine and the Vilsmeier salt. Compound (**1**) has been prepared once before[3] in connection with n.m.r. studies, but has not been used in chemical investigations.

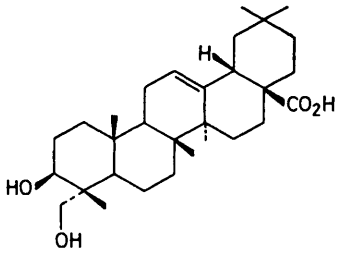
The following are examples of the synthetic utility of these bases. Hederagenin (**8**) in dimethylformamide re-

† All new compounds were characterised by microanalyses, n.m.r., mass spectroscopy *etc.*



(**1**); R^1 = Bu^t, R^2 = R^3 = Me
(**2**); R^1 = Bu^t, R^2 = R^3 = Et
(**3**); R^1 = Bu^t, R^2 = Et, R^3 = Pr^i
(**4**); R^1 = H, R^2 = R^3 = Pr^i
(**5**); R^1 = Et, R^2 = R^3 = Pr^i
(**6**); R^1 = Bu^t, R^2 = R^3 = Pr^i
(**7**); R^1 = R^2 = R^3 = Pr^i

acted rapidly at room temperature with methyl iodide in the presence of base (**1**) to give the methyl ester (88%). Adamantane-1-carboxylic acid in benzene was likewise immediately isopropylated with Pr^{i}I at room temperature to give the isopropyl ester (91%).



(**8**)

Heating cholestan-3β-yl tosylate (toluene-*p*-sulphonate) with bases (**3**) or (**7**) at 120 °C for 24 h gave a mixture of cholest-2- and -3-enes (80—85%), which compares favourably with the literature method (collidine, 170 °C, 6 h, 63%).[4] In contrast 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) gave only 31% of the mixed cholestenes but at a lower temperature (80—90 °C).

Alkylation of ethyl acetoacetate (1 equiv.) with MeI (2 equiv.) and base (**1**) (1 equiv.) at room temperature in ether gave, after 5 min, the 2-methylated compound (83%) predominantly. Treatment of this under the same conditions with base (**1**) (1·34 equiv.) gave the 2,2-dimethyl compound (83%).

TABLE

Compound	I.r. (film) ν_{max}/cm^{-1}	Methylation, $t_{1/2}$[a]/min	Benzylation, $t_{1/2}$[b]/min
(**1**)	1620	<5	5—6
(**2**)	1620	<5	11
(**3**)	1615	7	9 h
(**4**)	1590	—	—
(**5**)	1610	15	very slow
(**6**)	1625	—	—
(**7**)	1605	210	(trace, 168 h)
DBN	—	<2	<2

[a] 0·5 M base and MeI (3 equiv.) in $CDCl_3$ at room temperature, determined by n.m.r. [b] 1 M base and benzyl bromide (3 equiv.) in $CDCl_3$ at room temperature, determined by n.m.r.

Preliminary data on the rates of alkylation of these bases have been obtained (Table). Bases (**1**), (**2**), (**3**), (**5**), and (**7**) are methylated more slowly than DBN and the behaviour of (**7**) is particularly favourable. The benzylation rates are comparable, base (**7**) being hardly alkylated after 168 h. For comparison Hunig's base (di-isopropylethylamine) was half-benzylated in 48 h.

(*Received*, 21*st July* 1981; *Com.* 873.)

[1] *Inter alia*, M. W. Rathke and R. Kow, *J. Am. Chem. Soc.*, 1972, **94**, 6854; R. A. Olofson and C. M. Dougherty, *ibid.*, 1973, **95**, 581, 582; N. C. Deno, E. J. Gladfelter, and D. G. Pohl, *J. Org. Chem.*, 1979, **44**, 3728; T. G. Back and D. H. R. Barton, *J. Chem. Soc., Perkin Trans.* 1, 1977, 924; G. Eisele and G. Simchen, *Synthesis*, 1978, 757; P. J. Stang and W. Treptow, *ibid.*, 1980, 283; R. W. Alder, N. C. Goode, N. Miller, F. Hibbert, K. P. P. Hunte, and H. J. Robbins, *J. Chem. Soc., Chem. Commun.*, 1978, 89.
[2] F. Heinzer, M. Soukup, and A. Eschenmoser, *Helv. Chim. Acta*, 1978, **61**, 2851; D. Sternbach, M. Shibuya, F. Jaisli, M. Bonetti, and A. Eschenmoser, *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 634; N. Ono, T. Yamada, T. Saito, K. Tanaka, and A. Kaji, *Bull. Chem. Soc. Jpn.*, 1978, **51**, 2401; N. Ono, T. Yoshimura, T. Saito, R. Tamura, R. Tanikaga, and A. Kaji, *ibid.*, 1979, **52**, 1716.
[3] H. Kessler, D. Leibfritz, and C. Burk, *Tetrahedron*, 1970, **26**, 1805.
[4] C. C. Beard in 'Organic Reactions in Steroid Chemistry,' eds. J. Fried and J. A. Edwards, Van Nostrand Reinhold, New York, 1972, vol. 1, p. 344.