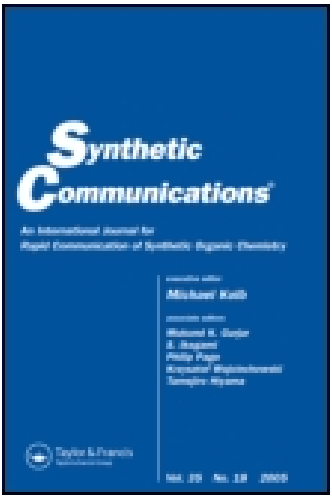

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An Efficient Synthesis of N-Aroyl-3-Phenyltetrahydropyridines

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AN EFFICIENT SYNTHESIS OF N-AROYL-3-PHENYLTETRAHYDROPYRIDINES

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Abstract: N-Aroyl-3-phenyltetrahydropyridines were conveniently synthesized by dehydration of N-aroyl-3-hydroxy-3-phenylpiperidines with toluenesulfonic acid on silica gel as a dehydration reagent.

Osteoporosis affects 25 million people, primarily women and contributes to 1.5 million fractures annually.[1,2] Although various agents are available or in clinical trials, most of them are bone absorption inhibitors. We were interested in finding novel non-steroidal compounds which promote bone formation. In previous studies Combs et al, had identified a series of tetrahydropyridazines (**A**) as a novel series of non-steroidal heterocycles. These compounds display cell-type selective, high affinity (nanomolar) binding to the progesterone receptors from TE85 osteosarcoma cells, but had greater than 1 μM binding affinity to the progesterone receptors from T47D and ZR75 human breast carcinoma cells.[3] Unfortunately, these compounds are metabolically unstable in *in vivo* studies. We then designed a series of tetrahydropyridines (**B**) to improve the metabolic profiles

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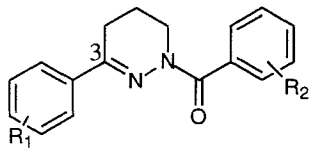
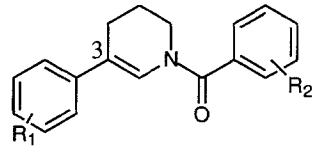
since carbon 3 in the heterocyclic ring is converted from an electrophilic site in the tetrahydropyridazine to a nucleophilic site in the tetrahydropyridine. Herein we report the synthesis of novel tetrahydropyridine derivatives by dehydration of 3-hydroxypiperidine precursors.



A



B

While two syntheses are described, [4,5] no general methods are available for the synthesis of N-acyl-3-aryltetrahydropyridines. Our targets, N-aroyl-3-phenyl-tetrahydropiperidines are novel compounds and a general method suitable for synthesis of a series of derivatives is needed. We decided to prepare this class of compounds from N-benzyl-3-piperidone by Grignard reaction, debenzylation, acylation and dehydration of the 3-piperidol precursors. Thus, addition of phenylmagnesium chloride (**1**) to the carbonyl group of N-benzyl-3-piperidone (**2**) gave N-benzyl-3-hydroxy-3-phenylpiperidine (**3**). 3-Hydroxy-3-phenylpiperidine (**4**) was obtained in nearly quantitative yields by hydrogenolysis of **3**. Compound **4** was acylated with various substituted aroyl chlorides to give a series of N-aroyl-3-hydroxy-3-phenylpiperidines (**5**, Table I). Variable temperature ^{1}H-NMR experiments of **5b** in DMSO suggest that there is hindered rotation about the amide bond in **5**.

The dehydration of the N-aroyl-3-piperidols was the key step in the reaction series. Our initial attempts to dehydrate **5** with various reagents, such as toluenesulfonic acid, acetic acid/acetyl cholride and oxalic acid, [6,7] gave **6** and **7** in low yields although N-alkyltetrahydropyridines have been prepared under similar

Table I. Experimental Data for 3-Phenyl-3-piperidols

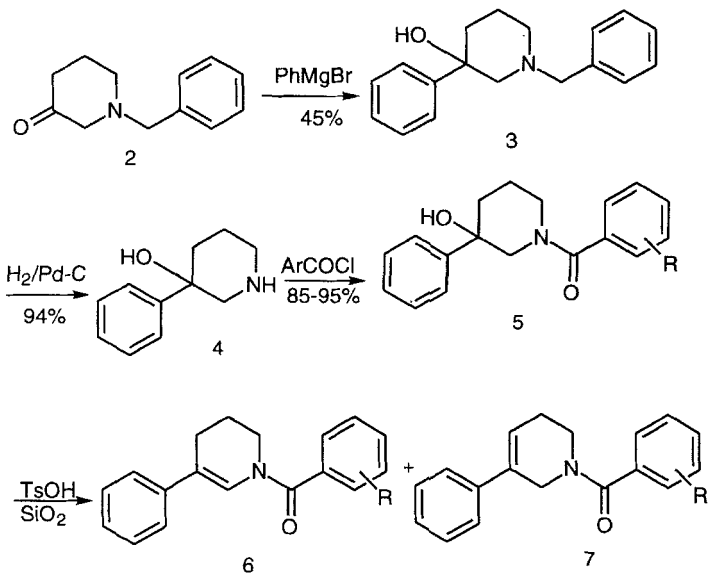
Product	R	Formula	Yields (%)	mp (°C)
5a	H	$C_{18}H_{19}NO_2$	91	125-126
5b	3,4-di-Cl	$C_{18}H_{17}Cl_2NO_2$	98	179-180
5c	4-NO_2	$C_{18}H_{18}N_2O_4$	96	185-186
5d	3,5-di-Cl	$C_{18}H_{17}Cl_2NO_2$	94	150-151
5e	3,4-di-Br	$C_{18}H_{17}Br_2NO_2$	98	176-177
5f	4-I	$C_{18}H_{18}INO_2$	95	188-189
5g	4-Ph	$C_{24}H_{23}NO_2$	94	162-163
5h	4-tBu	$C_{22}H_{27}NO_2$	95	184-185
5i	4-Bu	$C_{22}H_{27}NO_2$	91	140-141
5j	4-Cl	$C_{18}H_{18}ClNO_2$	95	164-165
5k	3-Cl	$C_{18}H_{18}ClNO_2$	89	120-121
5m	3,4-di-Me	$C_{20}H_{23}NO_2$	95	152-153
5n	3,4-di-NO_2	$C_{18}H_{17}N_3O_6$	95	174-175

Table II. Experimental Data for Tetrahydropyridines

Product	R	Formula	mp **6/7** (°C)	Yields **6/7** (Total) %
6a/7a	H	$C_{18}H_{17}NO$	109-110/124-126	8/18 * (26)
6b/7b	3,4-di-Cl	$C_{18}H_{15}Cl_2NO$	104-105/101-102	28/14 * (42)
6c/7c	4-NO_2	$C_{18}H_{16}N_2O_3$	140-142/134-135	61/37 (98)
6d/7d	3,5-di-Cl	$C_{18}H_{15}Cl_2NO$	110-111/99-100	55/37 (92)
6e/7e	3,4-di-Br	$C_{18}H_{15}Br_2NO$	148-149/132-134	52/15 (67)
6f/7f	4-I	$C_{18}H_{16}INO$	174-175/162-163	63/22 (85)
6g/7g	4-Ph	$C_{24}H_{21}NO$	170-171/168-169	60/38 (98)
6h/7h	4-tBu	$C_{22}H_{25}NO$	115-116/118-119	58/27 (95)
6i/7i	4-Bu	$C_{22}H_{25}NO$	oil/53-54	61/27 (88)
6j/7j	4-Cl	$C_{18}H_{16}ClNO$	154-155/123-124	63/23 (86)
6k/7k	3-Cl	$C_{18}H_{16}ClNO$	128-129/78-79	60/27 (87)
6m/7m	3,4-di-Me	$C_{20}H_{21}NO$	141-142/100-101	60/27 (87)
6n/7n	3,4-di-NO_2	$C_{18}H_{15}N_3O_5$	143-145/176-178	59/28 (87)

* Using oxalic acid.

conditions. [8-11] The low yield probably is due to concomitant hydrolysis of the amide bond. We then employed a toluenesulfonic acid/silica gel method which had previously shown utility in steroid synthesis. [12] First, toluenesulfonic acid was preadsorbed on to silica gel. The 3-piperidols (**5**) were heated in the presence of the silica gel in toluene. Although boiling benzene (80°C) was enough for the dehydration, toluene was used for safety reasons. The 1,4,5,6- and 1,2,5,6-tetrahydropyridine derivatives (**6** & **7**) were obtained in good total yields (Table II). Compounds **6** and **7** can be easily isolated by column chromatography in which **6** always has higher R_f value. The ratio of **6** and **7** is usually about 3:1 (Scheme I). The substituents on the benzoyl ring do not have much influence on the ratio of the two isomers. The spectral and analytical data of the 3-phenyl-3-piperidols and the tetrahydropyridines prepared are shown in Tables III-VI.



Scheme I

Table III. Spectral Data for the 3-Phenyl-3-piperidols

Product	MS $[M+1]^+$	IR (KBr) ν (cm^{-1})	^1H NMR (DMSO-d_6/TMS), δ, J (Hz)
5a	282	3424, 1631	7.57-7.22 (m, 10H, Ar), 5.18 (br, 1H), 4.50/4.17 & 3.40/3.30 (4d, J =12, 2H), 3.19/2.86 (2t, J =13, 2H), 2.12-1.99 (m, 2H), 1.77/1.60 (2d, J = 13, 2H)
5b	350	3442, 1601	7.74-7.22 (m, 8H), 5.27 (br, 1H), 4.50/4.17 & 3.40/3.30 (4d, J =12, 2H), 3.19/2.86 (2t, J =13, 2H), 2.12-1.99 (m, 2H), 1.77/1.60 (2d, J = 13, 2H)
5c	327	3362, 1619	8.25 (d, J = 8, 2H), 7.65 (d, J = 8, 2H), 7.40-7.25 (m, 5H), 5.30 (br, 1H), 4.58/4.22 (4d, J =12, 1H), 3.45 (t, J =12, 1H), 3.19/2.86 (2t, J =13, 2H), 2.12-1.99 (m, 2H), 1.77/1.60 (2d, J = 13, 2H)
5d	351	3422, 1622	7.75-7.20 (m, 8H), 5.33/5.25 (2s, 1H), 4.50/4.20 & 3.60/3.40 (4d, J =12, 2H), 3.19/2.86 (2t, J =13, 2H), 2.12-1.99 (m, 2H), 1.77/1.60 (2d, J = 13, 2H)
5e	440	3443, 1602	7.80 (s, 1H), 7.75 (d, J = 8, 1H), 7.55-7.15 (m, 6H), 5.33/5.25 (2s, 1H), 4.50/4.20 & 3.60/3.40 (4d, J =12, 2H), 3.19/2.86 (2t, J =13, 2H), 2.12-1.99 (m, 2H), 1.77/1.60 (2d, J = 13, 2H)
5f	407	3396, 1612	7.75 (d, J = 8, 2H), 7.65-7.15 (m, 7H), 5.30 (br, 1H), 4.55/4.18 (4d, J =12, 1H), 3.45/3.25 (2d, J = 12, 1H), 3.19/2.86 (2t, J = 13, 2H), 2.12-1.99 (m, 2H), 1.77/1.60 (2d, J = 13, 2H)
5g	358	3381, 1617	7.80 (m, 14H), 5.22 (s, 1H), 4.58/4.22 (4d, J =12, 1H), 3.45/3.25 (2d, J =12, 1H), 3.19/2.86 (2t, J =13, 2H), 2.12-1.99 (m, 2H), 1.77/1.60 (2d, J = 13, 2H)
5h	338	3411, 2964	7.75-7.20 (m, 9H), 5.19 (s, 1H), 4.50/4.20 & 3.60/3.40 (4d, J =12, 2H), 3.19/2.86 (2t, J =13, 2H), 2.12-1.99 (m, 2H), 1.77/1.60 (2d, J = 13, 2H), 1.26 (s, 9H)
5i	338	3424, 1602	7.75-7.20 (m, 9H), 5.19 (s, 1H), 4.50/4.20 & 3.60/3.40 (4d, J =12, 2H), 3.19/2.86 (2t, J =13, 2H), 2.55 (t, J = 8, 2H), 2.12-1.99 (m, 2H), 1.77/1.60 (2d, J = 13, 2H), 1.59 (m, 2H), 1.32 (m, 2H), 0.96 (t, J = 8, 3H),
5j	316	3370, 1634	7.60-7.20 (m, 9H), 5.21 (br, 1H), 4.58/4.15 & 3.60/3.40 (4d, J =12, 2H), 3.19/2.86 (2t, J =13, 2H), 2.12-1.99 (m, 2H), 1.77/1.60 (2d, J = 13, 2H)
5k	316	3431, 1602	7.60-7.20 (m, 9H), 5.22 (br, 1H), 4.58/4.15 & 3.60/3.40 (4d, J =12, 2H), 3.19/2.86 (2t, J =13, 2H), 2.12-1.99 (m, 2H), 1.77/1.60 (2d, J = 13, 2H)
5m	310	3435, 1598	7.60-7.20 (m, 9H), 5.22 (br, 1H), 4.58/4.15 & 3.60/3.40 (4d, J =12, 2H), 3.19/2.86 (2t, J =13, 2H), 2.25 (s, 6H), 2.12-1.99 (m, 2H), 1.77/1.60 (2d, J = 13, 2H)
5n	372	3380, 1630	8.32 (s, 1H), 8.25 (d, J = 10, 1H), 8.05 (d, J = 10, 1H), 7.60-7.20 (m, 9H), 5.38 (br, 1H), 4.58/4.20 & 3.60/3.40 (4d, J =12, 2H), 3.19/2.86 (2t, J =13, 2H), 2.12-1.99 (m, 2H), 1.77/1.60 (2d, J = 13, 2H)

Table IV. Spectral Data for the 1,4,5,6-Tetrahydropyridines

Product	MS $[M+1]^+$	IR (KBr) ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS), δ, J (Hz)
6a	264	2950, 1628	7.47-7.13 (m, 10H), 6.90 (s, 1H), 3.84/3.57 (2m, 2H), 2.49 (t, J = 8, 2H), 2.05/1.90 (2m, 2H)
6b	332	2965, 1626	7.68-7.14 (m, 8H), 6.78 (s, 1H), 3.80/3.57 (2m, 2H), 2.49 (t, J = 5, 2H), 2.04/1.91 (2m, 2H)
6c	309	1627, 1600	8.22 (d, J = 8, 2H), 7.64 (d, J = 8, 2H), 7.40-7.05 (m, 5H), 6.65 (s, 1H), 3.85/3.55 (2t, J = 7, 2H), 2.50 (t, J = 7, 2H), 2.05/1.91 (2m, 2H)
6d	332	1639, 1564	7.38-7.14 (m, 8H), 6.73 (s, 1H), 3.79/3.50 (2t, J = 7, 2H), 2.48 (t, J = 7, 2H), 2.02/1.90 (2m, 2H)
6e	422	1633, 1582	7.70 (d, J = 8, 1H), 7.55-7.15 (m, 7H), 6.85 (s, 1H), 3.79/3.50 (2t, J = 7, 2H), 2.48 (t, J = 7, 2H), 2.02/1.90 (2m, 2H)
6f	390	1629, 1583	7.80 (d, J = 8, 2H), 7.35-7.15 (m, 7H), 6.85 (s, 1H), 3.79/3.50 (2t, J = 7, 2H), 2.48 (t, J = 7, 2H), 2.02/1.90 (2m, 2H)
6g	340	1624, 1514	7.70-7.20 (m, 14H), 7.02 (s, 1H), 3.79/3.50 (2m, 2H), 2.48 (t, J = 7, 2H), 2.02/1.90 (2m, 2H)
6h	320	2951, 1631	7.70-7.20 (m, 14H), 7.02 (s, 1H), 3.80/3.50 (2m, 2H), 2.50 (t, J = 7, 2H), 2.02/1.90 (2m, 2H), 1.35 (s, 9H)
6i	320	2954, 2930	7.50-7.15 (m, 9H), 7.00 (s, 1H), 3.80/3.50 (2m, 2H), 2.62 (t, J = 8, 2H), 2.50 (t, J = 7, 2H), 2.02/1.90 (2m, 2H), 1.65 (m, 2H), 1.35 (m, 2H), 0.95 (t, J = 8, 3H)
6j	298	1632, 1594	7.55-7.15 (m, 9H), 6.85 (s, 1H), 3.90/3.60 (2m, 2H), 2.55 (t, J = 7, 2H), 2.10/1.90 (2m, 2H)
6k	298	1631, 1594	7.60-7.15 (m, 9H), 6.82 (s, 1H), 3.92/3.62 (2m, 2H), 2.55 (t, J = 7, 2H), 2.10/1.90 (2m, 2H)
6m	292	2948, 1619	7.35-7.15 (m, 8H), 7.02 (s, 1H), 3.90/3.60 (2m, 2H), 2.55 (t, J = 7, 2H), 2.36 (s, 3H), 2.35 (s, 3H), 2.10/1.90 (2m, 2H)
6n	354	1629, 1595	8.15 (s, 1H), 8.05 (d, J = 8, 1H), 7.95 (d, J = 8, 1H), 7.45-7.20 (m, 5H), 6.70 (s, 1H), 3.90/3.60 (2t, J = 7, 2H), 2.60 (t, J = 7, 2H), 2.02/1.90 (2m, 2H)

The reasons why toluenesulfonic acid/silica gel effects the dehydration while a solution of toluenesulfonic acid failed are not clear. One possibility is that water generated from the dehydration is adsorbed onto the silica gel. This decreases the chance for the hydrolysis of the products. Secondly, the more polar alcohols may reside on silica gel to a greater extent than the less polar olefinic

Table V. Spectra Data for the 1,2,5,6-Tetrahydropyridines

Product	MS $[M+1]^+$	IR (KBr) ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS), δ, J (Hz)
7a	264	1611, 1574	7.45-7.20 (m, 10H), 6.18 (t, J = 4, 1H), 4.55/4.25 (2m, 2H), 3.85/3.45 (2m, 2H), 2.35 (m, 2H)
7b	332	------	7.51-7.13 (m, 8H), 6.17 (t, J = 4, 1H), 4.51/4.19 (2m, 2H), 3.82/3.46 (2m, 2H), 2.31 (m, 2H)
7c	309	1655, 1628	8.50 (d, J = 8, 2H), 7.62 (d, J = 8, 2H), 7.45-7.15 (m, 5H), 6.25 (t, J = 4, 1H), 4.60/4.20 (2m, 2H), 3.85/3.45 (2m, 2H), 2.35 (m, 2H)
7d	332	1636, 1562	7.43-7.20 (m, 8H), 6.23 (t, J = 4, 1H), 4.58/4.23 (2m, 2H), 3.89/3.52 (2m, 2H), 2.37 (m, 2H)
7e	422	1651, 1618	7.75 (s, 1H), 7.65 (d, J = 8, 1H), 7.55-7.15 (m, 6H), 6.25 (t, J = 4, 1H), 4.58/4.22 (2m, 2H), 3.85/3.45 (2m, 2H), 2.35 (m, 2H)
7f	390	1650, 1627,	7.80 (d, J = 8, 1H), 7.55-7.15 (m, 6H), 6.22 (t, J = 4, 1H), 4.58/4.25 (2m, 2H), 3.85/3.45 (2m, 2H), 2.35 (m, 2H)
7g	340	1652, 1627	7.65-7.20 (m, 14H), 6.25 (t, J = 4, 1H), 4.58/4.25 (2m, 2H), 3.85/3.45 (2m, 2H), 2.35 (m, 2H)
7h	320	2957, 1652	7.50-7.20 (m, 9H), 6.25 (t, J = 4, 1H), 4.60/4.25 (2m, 2H), 3.85/3.45 (2m, 2H), 2.35 (m, 2H), 1.35 (s, 9H)
7i	320	2962, 2926	7.45-7.20 (m, 9H), 6.25 (t, J = 4, 1H), 4.60/4.25 (2m, 2H), 3.85/3.45 (2m, 2H), 2.50 (t, J = 7, 2H), 2.35 (m, 2H), 1.65 (m, 2H), 1.35 (m, 2H), 0.95 (t, J = 8, 3H)
7j	298	1654, 1633	7.40-7.20 (m, 9H), 6.18 (t, J = 4, 1H), 4.55/4.20 (2m, 2H), 3.80/3.45 (2m, 2H), 2.35 (m, 2H)
7k	298	1654, 1621	7.45-7.15 (m, 9H), 6.22 (t, J = 4, 1H), 4.58/4.25 (2m, 2H), 3.90/3.45 (2m, 2H), 2.40 (m, 2H)
7m	292	2921, 1647	7.50-7.15 (m, 9H), 6.22 (t, J = 4, 1H), 4.60/4.30 (2m, 2H), 3.90/3.60 (2m, 2H), 2.38 (m, 2H), 2.30 (s, 6H)
7n	354	1654, 1627	8.10 (s, 1H), 8.08 (d, J = 8, 1H), 7.80 (d, J = 8, 1H), 7.40-7.15 (m, 5H), 6.25 (t, J = 4, 1H), 4.60/4.25 (2m, 2H), 3.90/3.60 (2m, 2H), 2.35 (m, 2H)

products. Since the water concentration is low in solution, the hydrolysis of the products is then suppressed. Thirdly, from mechanistic point of view, acid catalyzed hydrolysis of amide bonds involves more reaction steps than dehydration of tertiary alcohols under acidic conditions. Each of these steps requires contact of a molecule or an intermediate with the solid phase since the reactions probably

Table VI. Analytical Data for 3-Phenyl-3-piperidols and Tetrahydropyridines

Product	C, H, N (% Calc.)	C, H, N (% Found)	Product	C, H, N (% Calc.)	C, H, N (% Found)
5a	76.84, 6.81, 4.98	76.91, 6.93, 5.01	**6h**	82.72, 7.89, 4.38	82.67, 7.87, 4.36
5b	61.73, 4.89, 4.00	61.63, 4.94, 3.90	**6i**	82.72, 7.89, 4.38	82.92, 7.84, 4.37
5c	66.25, 5.56, 8.58	66.11, 5.53, 8.47	**6j**	72.60, 5.42, 4.70	72.32, 5.46, 4.73
5d	61.73, 4.89, 4.00	61.55, 4.86, 3.93	**6k**	72.60, 5.42, 4.70	72.47, 5.36, 4.95
5e	49.23, 3.90, 3.19	49.58, 3.95, 3.07	**6m**	82.44, 7.26, 4.81	82.46, 7.24, 4.76
5f	53.09, 4.46, 3.44	53.05, 4.52, 3.34	**6n**	58.22, 4.61, 11.26	58.17, 4.58, 11.26
5g	80.64, 6.49, 3.92	80.64, 6.45, 3.94	**7a***	81.54, 6.54, 5.28	81.64, 6.48, 5.19
5h	78.30, 8.06, 4.15	78.03, 7.91, 4.32	**7b**	65.07, 4.55, 4.22	64.94, 4.60, 4.12
5i	78.30, 8.06, 4.15	78.40, 8.15, 3.93	**7c**	70.12, 5.23, 9.09	69.96, 5.13, 9.03
5j	68.46, 5.75, 4.44	68.27, 5.71, 4.34	**7d**	65.07, 4.55, 4.22	64.94, 4.38, 4.12
5k	68.46, 5.75, 4.44	68.55, 5.71, 4.37	**7e**	51.34, 3.59, 3.33	51.17, 3.50, 3.15
5m	77.64, 7.49, 4.55	77.23, 7.51, 4.36	**7f**	55.54, 4.14, 3.60	55.52, 3.98, 3.49
5n	58.22, 4.61, 11.32	58.17, 4.58, 11.26	**7g**	84.92, 6.24, 4.13	84.70, 6.21, 4.06
6a	82.10, 6.51, 5.32	81.75, 6.54, 5.18	**7h**	82.72, 7.89, 4.38	82.51, 7.77, 4.40
6b*	64.72, 4.59, 4.19	64.48, 4.57, 4.22	**7i**	82.72, 7.89, 4.38	82.42, 7.90, 4.31
6c	70.12, 5.23, 9.09	69.85, 5.13, 9.03	**7j**	72.60, 5.42, 4.70	72.43, 5.43, 4.54
6d	65.07, 4.55, 4.22	64.92, 4.42, 4.09	**7k**	72.60, 5.42, 4.70	72.48, 5.32, 4.67
6e	51.34, 3.59, 3.33	51.73, 3.51, 3.22	**7m**	82.44, 7.26, 4.81	82.06, 7.19, 4.69
6f	55.54, 4.14, 3.60	55.61, 4.18, 3.46	**7n**	58.22, 4.61, 11.26	60.84, 4.27, 11.62
6g	84.92, 6.24, 4.13	84.77, 6.34, 4.06			

* contains 0.1 hydrate

occur on the surface of silica gel. Therefore, the relative rate of dehydration is higher than that of hydrolysis.

We found that long reaction times favor the more thermostable isomer **6**. For example, when **5c** was reacted at the same temperature for 72h instead of 1h, only the thermostable product **6c** was obtained (84% yield). Therefore, it is likely

that **6** and **7** are interconvertable under these reaction conditions via the benzyl cation intermediate.

EXPERIMENTAL

Melting points were determined with a Thomas capillary melting point apparatus and are uncorrected. Satisfactory NMR and IR spectra were obtained for all compounds. Proton NMR spectra were recorded at 300 MHz on a QE-300 instrument. Infrared spectra were run on a Perkin-Elmer 1650 instrument. Mass spectra (CI) were measured with a INCOS 50 spectrometer. Elemental analyses were carried out at Qualitative Technologies Inc., Whitehouse, NJ.

N-Benzyl-3-hydroxy-3-phenylpiperidine (3):

To a solution of phenylmagnesium chloride (2.0M in THF, 10 ml, 20 mmol) in THF (dry, 50 ml) a solution of N-benzyl-3-piperidone (3.3 g, 17.4 mmol) in THF (dry, 50 ml) was added at -5 °C. The mixture was stirred at rt for 16 hr and then quenched with sat. ammonium chloride, extracted with ethyl acetate. The organic phase was washed with brine and dried with magnesium sulfate. Column chromatography (silica gel, hexane:ethyl acetate = 4:1) gave 2.09 g (45%) of the title compound as a white solid; mp 73.5-74.5 °C (Lit. 11, mp 71-73 °C).

$C_{18}H_{21}NO$ (267.37)	calc.	C 80.86	H 7.92	N 5.24
	found	C 80.92	H 7.88	N 5.21

3-Hydroxy-3-phenylpiperidine (4):

To a solution of **3** (2 g, 7.48 mmol) in methanol (30 ml) Pd-C (10%, 30 mg) was added. The mixture was hydrogenated at 30 PSI for 10 hr and filtered through celite. After evaporation of the solvent and drying under vacuum the title

compound was isolated as a white solid (1.24 g, 94%); mp: 84-86°C (Lit. 11, mp 86-88 °C).

$C_{11}H_{15}NO$ (177.25)	calc.	C 74.54	H 8.53	N 7.90
	found	C 74.26	H 8.50	N 7.75

N-Benzoyl-3-hydroxy-3-phenylpiperidine (5a), a general procedure: To a solution of **4** (310 mg, 1.75 mmol) in THF (30 ml) and pyridine (dry, 0.5 ml), benzoyl chloride (203 ml, 1.75 mmol) was added. The mixture was stirred at rt for 2.5 hr and quenched with water. The organic phase was washed with 0.5 N HCl, brine, sat. sodium bicarbonate and brine sequentially, and dried with magnesium sulfate. The solvent was evaporated and the residue was dried under vacuum. The title compound was obtained as a white solid. Yields and melting points are summarized in Table I.

N-(3,5-Dichlorobenzoyl)-3-phenyl-1,4,5,6-tetrahydropyridine (6b) and N-(3,5-Dichlorobenzoyl)-3-phenyl-1,2,5,6-tetrahydropyridine (7b), a general procedure:

Silica gel (50 g, 70-230 mesh) was added to a solution of toluenesulfonic acid hydrate (1.5 g) in 150 ml of acetone. After stirring for 30 min the solvent was removed and the silica gel was dried under vacuum. The silica gel prepared above (5 g) was added to a solution of **5b** (200 mg, 0.57 mmol) in toluene (30 ml). The mixture was heated at 80°C for 2 hr. The solvent was evaporated and the residue was directly loaded on a column (silica gel, hexane:ethyl acetate = 1:9). The title compounds were isolated. Yields and melting points are summarized in Table III.

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