Sterically Crowded Amines

Acyclic and Heterocyclic Condensation Products from α-Aminoketones and Benzaldehyde

G. F. HENNION and GEORGE G. KING[1]
The Chemical Laboratories, University of Notre Dame, Notre Dame, Ind.

α,β-Unsaturated aminoketones, $R^1R^2C(NR^3R^4)—CO—CH{=}CH—Ar$ (I), bright yellow but giving colorless hydrochloride salts, were prepared by the Claisen-Schmidt condensation of α-aminoketones, $R^1R^2C(NR^3R^4)—COCH_3$, with aromatic aldehydes. The products where R^4 = H were converted to the corresponding 1,2,2-trialkyl-5-aryl-3-pyrrolidinones, $R^1R^2\overline{C—CO—CH_2CH(Ar)—N}R^3$ (II), by thermal cyclization and subsequently, by sodium borohydride reduction, to the corresponding 1,2,2-trialkyl-5-aryl-3-pyrrolidinols (III). Reduction of I by borohydride and via catalytic hydrogenation yielded assorted new α,β-unsaturated 1,2-aminoalcohols (IV), saturated aminoketones (V) and saturated 1,2-aminoalcohols (VI).

THE AVAILABILITY of sterically crowded aminoketones $R^1R^2C(NR^3R^4)—COCH_3$ prepared as described earlier (*1, 2, 4, 5*), prompted a study of the Claisen-Schmidt condensation (*6*) of these compounds with benzaldehyde and several para-substituted benzaldehydes. The reaction products (Table I) were then converted to several new series of aminoketones and aminoalcohols as shown below (Figure 1) and described in Tables II to VI.

Table I. α,β-Unsaturated Aminoketones, $R^1R^2C(NR^3R^4)CO—CH{:}CH—C_6H_4X$

Cmpd.	R^1	R^2	R^3	R^4	X	M.P., ° C.[a]	Yield, %[b]
1	CH_3	CH_3	C_2H_5	H	H	82-83.5	89
2	CH_3	CH_3	C_2H_5	H	p-CH_3	66-68	94
3	CH_3	CH_3	C_2H_5	H	p-OCH_3	oil[d]	81
4	CH_3	CH_3	C_2H_5	H	p-Cl	62-64	88
5	CH_3	CH_3	iso-C_3H_7	H	H	56-57.5	95
6	CH_3	CH_3	*tert*-C_4H_9	H	H	93-94	94
7	CH_3	CH_3	CH_3	CH_3	H	oil[e]	91
8	CH_3	CH_3	CH_3	CH_3	p-CH_3	oil[f]	73
9	CH_3	CH_3	CH_3	CH_3	p-OCH_3	oil[g]	70
10	CH_3	CH_3	CH_3	CH_3	p-Cl	71-74	76
11	CH_3	C_2H_5	C_2H_5	H	H	51-52	96
12	$—CH_2(CH_2)_3CH_2—$		C_2H_5	H	H	50-51	86
13	$—CH_2(CH_2)_3CH_2—$		CH_3	CH_3	H	oil[h]	67

Hydrochlorides

Molecular formula	M.P., ° C.[c]	Carbon, % Calcd.	Carbon, % Obsd.	Hydrogen, % Calcd.	Hydrogen, % Obsd.	Nitrogen, % Calcd.	Nitrogen, % Obsd.
$C_{14}H_{20}ClNO$	202-203	66.26	66.34	7.94	8.08	5.52	5.72
$C_{15}H_{22}ClNO$	219-220	67.27	67.47	8.28	8.38	5.23	5.11
$C_{15}H_{22}ClNO_2$	229-230[i]	63.48	63.68	7.82	8.09	4.94	4.78
$C_{14}H_{19}Cl_2NO$	245-246[i]	58.34	58.64	6.64	6.72	4.86	4.72
$C_{15}H_{22}ClNO$	176-177	67.27	67.29	8.28	8.40	5.23	5.28
$C_{16}H_{24}ClNO$	208-209[i]	68.19	67.98	8.58	8.75	4.97	4.78
$C_{14}H_{20}ClNO$	173-175	66.26	66.49	7.94	8.11	5.52	5.48
$C_{15}H_{22}ClNO$	181-183	67.27	67.40	8.28	8.52	5.23	5.19
$C_{15}H_{22}ClNO_2$	189-191[i]	63.48	63.38	7.82	7.70	4.94	4.88
$C_{14}H_{19}Cl_2NO$	210-211	58.34	58.62	6.64	6.79	4.86	4.82
$C_{15}H_{22}ClNO$	167-168	67.27	67.13	8.28	8.39	5.23	5.40
$C_{17}H_{24}ClNO$	219-220	69.49	69.69	8.23	8.47	4.77	4.81
$C_{17}H_{24}ClNO$	159-162	69.49	69.59	8.23	8.36	4.77	4.69

[a] Melting points are for crystallized products. [b] Yields are for crude solids or once distilled oil. [c] Melting points for analytical samples. [d] Isolated as hydrochloride salt. [e] B.p. 150–155°/2.6 mm., n_D^{25} 1.5607. [f] B.p. 152–154°/2.3 mm., n_D^{25} 1.5635. [g] B.p. 179–181°/3.6 mm., n_D^{25} 1.5842. [h] B.p. 177–180°/1.9 mm., n_D^{25} 1.5785. [f] Melts with decomposition.

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[1] Present address: Olin Research Center, New Haven, Conn.

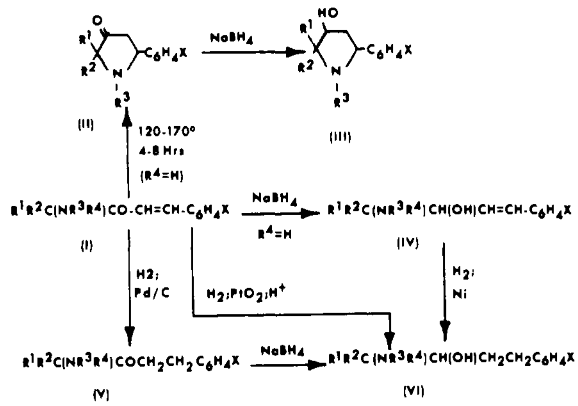

Figure 1. Some reactions of α,β-unsaturated aminoketones

Table II. 1,2,2-Trialkyl-5-aryl-3-pyrrolidinones, $R^1R^2C—CO—CH_2—CH(C_6H_4—X)—NR^3$

Cmpd.	R^1	R^2	R^3	X	B.P., ° C.[a]	Mm.	n^{25}_D	Yield, %[b]
14	CH_3	CH_3	CH_3	H	102–108	1.5[d]		70
15	CH_3	CH_3	C_2H_5	H	127–128	4.0	1.5170	79
16	CH_3	CH_3	C_2H_5	*p*-CH_3	124–126	1.9	1.5156	77
17	CH_3	CH_3	C_2H_5	*p*-OCH_3	144–146	1.5	1.5222	71
18	CH_3	CH_3	C_2H_5	*p*-Cl	130–131	1.1	1.5350	76
19	CH_3	CH_3	iso-C_3H_7	H	122–125	3.0[e]		80
20	CH_3	C_2H_5	C_2H_5	H	138–140	4.0	1.5173	85
21	$—CH_2(CH_2)_3CH_2—$		C_2H_5	H				94

Hydrochlorides

Molecular formula	M.P., ° C.[c]	Carbon, %		Hydrogen, %		Nitrogen, %	
		Calcd.	Obsd.	Calcd.	Obsd.	Calcd.	Obsd.
$C_{13}H_{17}NO$	62–63[g]	76.81	76.83	8.43	8.35	6.89	6.84
$C_{14}H_{20}ClNO$	192–194	66.26	66.44	7.94	8.03	5.52	5.81
$C_{15}H_{22}ClNO$	191–194	67.27	67.01	8.28	8.47	5.23	5.16
$C_{15}H_{22}ClNO_2$	167–170	63.48	63.69	7.82	8.11	4.94	4.66
$C_{14}H_{19}Cl_2NO$	181–183	58.34	58.45	6.64	6.72	4.86	4.82
$C_{15}H_{22}ClNO$	204–206	67.27	67.41	8.28	8.31	5.23	5.10
$C_{15}H_{22}ClNO$	174–175	67.27	67.46	8.28	8.34	5.23	5.28
$C_{17}H_{24}ClNO$	212–214	69.49	69.61	8.23	8.36	4.77	4.73

[a] Boiling points are for once distilled material. [b] Yields reported are for once distilled oil or crude solids. [c] Melting points are for analytical samples. [d] Distillate solidified in receiver, m.p. 59–66°. [e] Distillate solidified in receiver, m.p. 68–71°. [f] Isolated as hydrochloride salt. [g] Lit. (*3*) m.p. 71° C. Analysis of free base; hydrochloride salt too hygroscopic to handle.

Table III. 1,2,2-Trialkyl-5-aryl-3-pyrrolidinol Hydrochlorides, $R^1R^2C—CH(OH)—CH_2CH(C_6H_4—X)—NR^3 \cdot HCl$

Cmpd.	Origin[a]	M.P., ° C.[b]	Yield, %[c]	Molecular Formula	Carbon, %		Hydrogen, %		Nitrogen, %	
					Calcd.	Obsd.	Calcd.	Obsd.	Calcd.	Obsd.
22	15	169–171	65[d]	$C_{14}H_{22}ClNO$	65.73	65.85	8.67	8.75	5.48	5.32
23	16	181–184	84	$C_{16}H_{24}ClNO$	66.77	66.90	8.97	9.15	5.19	5.13
24	17	184–187	86	$C_{15}H_{24}ClNO_2$	63.03	63.21	8.46	8.73	4.90	4.82
25	18	165–168	76	$C_{14}H_{21}Cl_2NO$	57.93	57.98	7.29	7.56	4.83	4.75
26	19	162–165	60	$C_{15}H_{24}ClNO$	66.77	66.75	8.97	9.14	5.19	5.26
27	20	157–160	71		66.30	66.43	9.27	9.64	4.83	4.71
		159–162			65.62	65.96	9.30	9.41	4.78	4.62
28	21	230–232	62	$C_{17}H_{26}ClNO$	69.01	68.87	8.86	8.90	4.70	4.70

[a] Numbers correspond to compounds identified in Table II. [b] Melting points are for analytical samples. [c] Yields reported are for crude products. [d] Isolated by distillation of the free base, b.p. 142–143°/7.0 mm., n^{25}_D 1. 5277. [e] Analysis of compound crystallized from isopropanol appears to fit a molecular formula of $C_{15}H_{24}ClNO \cdot 1/3\ C_3H_8O$. [f] Analysis of compound crystallized from ethanol plus ether appears to fit a molecular formula of $C_{15}H_{24}ClNO \cdot 1/2\ C_2H_6O$.

Table IV. α,β-Unsaturated-1,2-Aminoalcohols $R^1R^2C(NR^3R^4)CH(OH)—CH{:}CH—C_6H_4—X$

						Hydrochlorides							
								Carbon, %		Hydrogen, %		Nitrogen, %	
Cmpd.	Origin[a]	M.P., °C.[b]	B.P., °C.[c]	Mm.	Yield, %[d]	Molecular formula	M.p., °C.[e]	Calcd.	Obsd.	Calcd.	Obsd.	Calcd.	Obsd.
29	1	82-83	170-174	10	54	$C_{14}H_{22}ClNO$	174-175	65.73	65.91	8.67	8.79	5.48	5.40
30	2	96-97	...	...	69	$C_{15}H_{24}ClNO$	195-197	66.77	66.57	8.97	9.22	5.19	5.06
31	5	85-86	...	...	58	$C_{15}H_{24}ClNO$	177-178	66.77	66.83	8.97	9.19	5.19	5.11
32	6	...	159-161	3.8	64	$C_{16}H_{26}ClNO$	194-196[f]	67.70	67.73	9.23	9.47	4.94	4.74
33	11	...	145-147	1.5	77	$C_{15}H_{24}ClNO$	179-180	66.77	66.60	8.97	9.19	5.19	5.21
34	12	...	182-184	3.0	78	$C_{17}H_{26}ClNO$	161-162	69.01	69.26	8.86	9.07	4.73	4.68

[a] Numbers refer to compounds identified in Table I. [b] Melting points are for recrystallized samples. [c] Boiling points for once-distilled samples. [d] Yields for crude solid or once-distilled material. [e] Melting points for analytical samples. [f] Melts with decomposition.

Table V. Saturated α-Aminoketone Hydrochlorides, $R^1R^2C(NR^3R^4)CO—CH_2—CH_2—C_6H_4—X \cdot HCl$

					Carbon, %		Hydrogen, %		Nitrogen, %	
Cmpd.	Origin[a]	M.p., °C.[b]	Yield, %[c]	Molecular Formula	Calcd.	Obsd.	Calcd.	Obsd.	Calcd.	Obsd.
35	1	170-171	89	$C_{14}H_{22}ClNO$	65.73	65.72	8.67	8.95	5.48	5.43
36	6	175-178[d]	95[e]	$C_{16}H_{26}ClNO$	67.70	67.57	9.23	9.18	4.94	4.65
37	7	131-133	85	$C_{14}H_{22}ClNO$	65.73	65.89	8.67	8.77	5.48	5.41
38	13	143-145	90	$C_{17}H_{26}ClNO$	69.01	69.20	8.86	8.75	4.73	4.55

[a] Numbers refer to compounds identified in Table I. [b] Melting points are for analytical samples. [c] Yields reported are for crude salts. [d] Melts with decomposition. [e] Isolated as the free base, m.p. 66–68°.

Table VI. Saturated 1,2-Aminoalcohol Hydrochlorides, $R^1R^2C(NR^3R^4)CH(OH)—CH_2—CH_2—C_6H_4—X \cdot HCl$

					Carbon, %		Hydrogen, %		Nitrogen, %	
Cmpd.	Method[a]	M.P., °C.[b]	Yield, %[c]	Molecular Formula	Calcd.	Obsd.	Calcd.	Obsd.	Calcd.	Obsd.
39	A,B,C,	192-194	95,91,74	$C_{14}H_{24}ClNO$	65.22	65.40	9.38	9.64	5.43	5.33
40	A	180-182[d]	90	$C_{15}H_{26}ClNO$	66.27	66.49	9.64	9.86	5.15	4.96
41[f]	A[e],B	137-140	95,97	$C_{14}H_{24}ClNO$	65.22	65.42	9.38	9.63	5.43	5.31
42	A,B	149-151	90,89	$C_{15}H_{26}ClNO$	66.27	66.43	9.64	9.67	5.15	5.08
43	A,B,C	187-188	92,93,81	$C_{16}H_{28}ClNO$	67.23	67.27	9.87	10.12	4.90	4.61
44	A	161-163	98	$C_{15}H_{26}ClNO$	66.27	66.43	9.64	9.67	5.15	5.08
45	A	187-188	94	$C_{17}H_{28}ClNO$	68.55	68.75	9.47	9.51	4.70	4.85
46[g]	A[e]	169-170	98	$C_{17}H_{28}ClNO$	68.55	68.76	9.47	9.53	4.70	4.81

[a] Method A: catalytic hydrogenation of corresponding α,β-unsaturated aminoalcohol (Table IV); method B: catalytic hydrogenation of corresponding α,β-unsaturated aminoketone hydrochloride (Table I); method C: sodium borohydride reduction of saturated aminoketone (Table V). [b] Melting points for analytical samples. [c] Yields of crude products. [d] Melts with decomposition. [e] Method A applied to mixture of saturated and unsaturated aminoalcohols obtained by prior borohydride reduction of unsaturated ketones. [f] Origin, compd. 7, Table I. [g] Origin, compd. 13, Table I.

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