Sterically Crowded Amines

Acyclic and Heterocyclic Condensation Products from α-Aminoketones and Benzaldehyde

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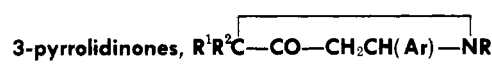
α,β-Unsaturated aminoketones, $R^1R^2C(NR^3R^4)—CO—CH{=}CH—Ar$ (I), bright yellow but giving colorless hydrochloride salts, were prepared by the Claisen-Schmidt condensation of α-aminoketones, $R^1R^2C(NR^3R^4)—COCH_3$, with aromatic aldehydes. The products where R^4 = H were converted to the corresponding 1,2,2-trialkyl-5-aryl-3-pyrrolidinones,  $R^1R^2C—CO—CH_2CH(Ar)—NR^3$ **(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.

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

Cmpd.	R^1	R^2	R^8	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, %		Hydrogen, %		Nitrogen, %	
		Calcd.	Obsd.	Calcd.	Obsd.	Calcd.	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. [i] Melts with decomposition.

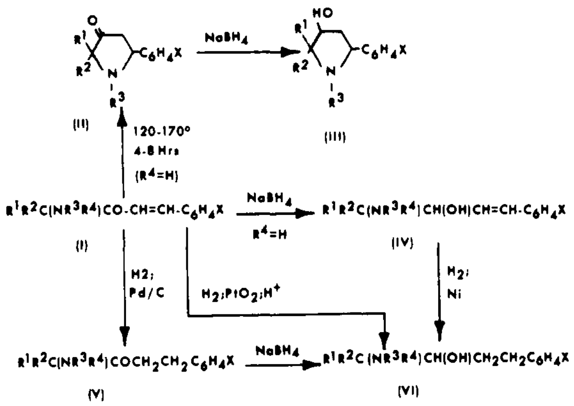

Figure 1. Some reactions of α,β-unsaturated aminoketones

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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