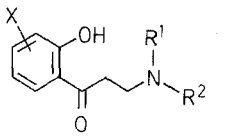

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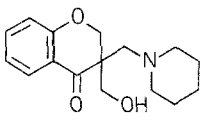

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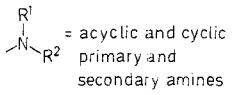
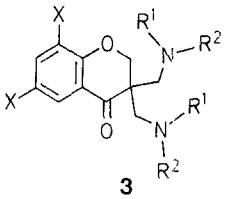


= acyclic and cyclic primary and secondary amines



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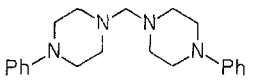
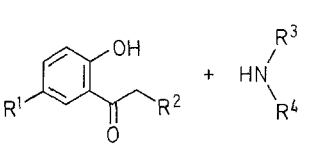
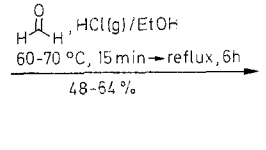


4

3	X	R^1	R^2
a	Br	$-(CH_2)_4-$	
b	Br	$-CH_2CH_2OCH_2CH_2-$	
c	Cl	CH_3	CH_3
d	Cl	$-(CH_2)_4-$	
f	Cl	$-(CH_2)_5-$	
g	Cl	$-CH_2CH_2OCH_2CH_2-$	



5-8 9



10-13

	R^1	R^2	9	R^3	R^4
5	H	H	a	$-CH_2CH_2OCH_2CH_2-$	
6	H	CH_3	b	$-(CH_2)_5-$	
7	H	C_2H_5	c	$-(CH_2)_4-$	
8	CH_3	Ph	d	C_2H_5	C_2H_5
			e	CH_3	CH_3

The Mannich Reaction of 1-(2-Hydroxyphenyl)-1-ethanone, -1-propanone and -1-butanone, and 1-(2-Hydroxy-5-methylphenyl)-2-phen-yl-1-ethanone

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The title compounds on reaction with secondary amines in the presence of formaldehyde under acidic condition, gave the corresponding Mannich bases by ω-aminomethylation.

1-(2-Hydroxyphenyl)ethanone **(5)** and its ring substituted derivatives are reported to undergo the normal aminomethylation at the ω-methyl group when treated with formaldehyde and primary[1,2] and secondary amines[3-8] to give **1**. However recently, unusual Mannich type reactions of **5** have been reported. In these reactions cyclic chromanone derivatives **2**[9] and **3**[10] are reported to be formed.

It was therefore, thought imperative to investigate the Mannich reaction of **5** as well as of its higher homologues, such as **6** and **7**. Moreover, the Mannich reaction of **8** was also studied as it contained a sufficiently active methylene group. The aim of the project was to investigate the possibility of the participation of the hydroxy group of the substrates in the ring formation.

Compounds **5, 6** and **7** were prepared by known methods,[11-13] whereas the procedure for the preparation of **8** was modified.[14]

Substrates **5–8** did not undergo the aminomethylation in the absence of an acidic catalyst. When 1-phenylpiperazine was used as amine, only **4** was obtained. On the other hand, when the reaction of **5** was carried out with a secondary amine and formaldehyde in the presence of gaseous hydrogen chloride or perchloric acid, 3-amino-1-(2-hydroxyphenyl)-1-propanones **(10)** were obtained (Table 1). Following the same procedure, **6, 7** and **8** gave 3-amino-1-(2-hydroxyphenyl)-2-methyl-1-propanones **(11)** (Table 2), 2-aminomethyl-1-(2-hydroxyphenyl)-1-butanones **(12)** (Table 3), and 3-amino-1-(2-hydroxy-5-methylphenyl)-2-phenyl-1-propanones **(13)** (Table 4), respectively.

Thus, **5, 6, 7,** and **8** reacted with secondary amines and formaldehyde to yield normal Mannich bases and not the cyclic chromanone derivatives as reported earlier.

Table 1. 3-Amino-1-(2-hydroxyphenyl)-1-propanones **10** Prepared

Product	Yield[a] (%)	mp (°C)[b]	Molecular Formula[c]	n	IR (neat) ν (cm^{-1}) OH	IR (neat) ν (cm^{-1}) C=O	^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)
10a	61	191–192	$C_{13}H_{17}NO_3$ (235.3)	1.493	3400–3200	1646	2.54 (t, 4H, J = 4, $N(CH_2)_2$); 2.85 (t, 2H, J = 7, CH_2); 3.22 (t, 2H, J = 7, $COCH_2$); 3.74 (t, 4H, J = 4, $O(CH_2)_2$); 6.85–7.85 (m, 4H, H_{arom}); 12.22 (br s, 1H, OH)
10b	63	154–155	$C_{14}H_{19}NO_2$ (233.3)	1.404	3600–3150	1640	
10c	59	145–146	$C_{13}H_{17}NO_2$ (219.3)	1.438	3500–3300	1655	
10d	64	173–174	$C_{13}H_{19}NO_2$ (221.3)	1.408	3550–3200	1640	
10e	60	oil	$C_{11}H_{15}NO_2$ (193.2)	1.401	3550–3150	1645	

[a] Yield of the free base is reported.
[b] mp of the hydrochloride is reported.
[c] Satisfactory microanalyses obtained: C ±0.13, H ±0.15, N ±0.1.

Table 2. 3-Amino-1-(2-hydroxyphenyl)-2-methyl-1-propanones **11** Prepared

Product	Yield[a] (%)	mp (°C)[b]	Molecular Formula[c]	n	IR (neat) ν (cm^{-1}) OH	IR (neat) ν (cm^{-1}) C=O	^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)
11a	53	160–161	$C_{14}H_{19}NO_3$ (249.3)	1.410	3400–3200	1634	1.25 (d, 3H, J = 7, CH_3); 2.44 (dd, 1H, J_{gem} = 12, J_{vic} = 8, N(CHaHb); 2.50 (t, 4H, J = 5, $N(CH_2)_2$); 2.90 (dd, 1H, J_{gem} = 12, J_{vic} = 8, N(CHaHb); 3.65 (t, 4H, J = 5, $O(CH_2)_2$); 3.65–4.00 (m, 1H, COCH); 6.90–7.90 (m, 4H, H_{arom}); 12.50 (s, 1H, OH)
11b	56	240–241	$C_{15}H_{21}NO_2$ (247.3)	1.468	3600–3250	1640	
11c	59	–	$C_{14}H_{19}NO_2$ (233.3)	1.403	3400–3200	1635	
11d	63	–	$C_{14}H_{21}NO_2$ (235.3)	1.413	3550–3300	1640	
11e	59	–	$C_{12}H_{17}NO_2$ (207.3)	1.467	3500–3100	1646	

[a] Yield of the free base is reported.
[b] mp of the hydrochloride is reported.
[c] Satisfactory microanalyses obtained: C ±0.1, H ±0.09, N ±0.06.

Table 3. 2-Aminomethyl-1-(2-hydroxyphenyl)-1-butanones **12** Prepared

Product	Yield[a] (%)	mp (°C)[b]	Molecular Formula[c]	n	IR (neat) ν (cm^{-1}) OH	IR (neat) ν (cm^{-1}) C=O	^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)
12a	48	155–156	$C_{15}H_{21}NO_3$ (263.3)	1.471	3600–3200	1630	
12b	51	235–236	$C_{16}H_{23}NO_2$ (261.4)	1.461	3500–3200	1630	
12c	49	162–163	$C_{15}H_{21}NO_2$ (247.3)	1.458	3600–3200	1642	
12d	51	237–238	$C_{15}H_{23}NO_2$ (249.3)	1.400	3600–3200	1630	
12e	50	–	$C_{13}H_{19}NO_2$ (221.3)	1.501	3550–3300	1640	0.92 (t, 3H, J = 6, CH_3); 1.30 (s, 6H, $N(CH_3)_2$); 1.30–1.90 (m, 2H, CH_2); 2.40 (dd, 1H, J_{gem} = 12, J_{vic} = 7, N(CHaHb); 2.90 (dd, 1H, J_{gem} = 12, J_{vic} = 7, $N(CH_aH_b)$; 3.30–3.90 (m, 1H, COCH); 6.70–7.90 (m, 4H, H_{arom})

[a] Yield of the free base is reported.
[b] mp of the hydrochloride is reported.
[c] Satisfactory microanalyses obtained: C ±0.16, H ±0.13, N ±0.1.

Table 4. 3-Amino-1-(2-hydroxy-5-methylphenyl)-2-phenyl-1-propanones **13** Prepared

Product	Yield[a] (%)	mp (°C)[b]	mp (°C)[c]	Molecular Formula[d]	IR (neat) ν (cm^{-1}) OH	IR (neat) ν (cm^{-1}) C=O	^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)
13a	48	57–58	191–192	$C_{20}H_{23}NO_3$ (325.4)	3500–3300	1640	2.24 (s, 3H, $ArCH_3$); 2.46 (t, 4H, J = 3.6, $N(CH_2)_2$); 2.60 (dd, 1H, J_{gem} = 10.8, J_{vic} = 9, CH_aH_b); 3.44 (dd, 1H, J_{gem} = 10.8, J_{vic} = 9, CH_aH_b); 3.60 (t, 4H, J = 3.6, $O(CH_2)_2$); 4.84 (q, 1H, J_{vic} = 9Hz, COCH); 6.70–7.55 (m, 8H, H_{arom}); 12.10 (s, 1H, OH)
13b	51	45–46	215–216	$C_{21}H_{25}NO_2$ (323.4)	3500–3300	1680	
13c	48	46–47	181–182	$C_{20}H_{23}NO_2$ (309.4)	3400–3100	1685	
13d	53	51–52	200–201	$C_{20}H_{25}NO_2$ (311.4)	3400–3200	1680	
13e	51	46–47	–	$C_{18}H_{21}NO_2$ (283.4)	3550–3250	1675	

[a] Yield of the free base is reported.
[b] mp of the free base is reported.
[c] mp of the hydrochloride is reported.
[d] Satisfactory microanalyses obtained: C ±0.15, H ±0.17, N ±0.11.

All reagents were commercially available. Secondary amines used for the reaction were morpholine, piperidine, pyrrolidine, diethylamine and dimethylamine. Melting points were recorded on a Campbell precision melting point apparatus in open capillaries and are uncorrected. For column chromatography, silica gel (60–120 mesh, Acme grade) was used. The IR spectra were obtained using a Perkin-Elmer 397 spectrophotometer. ^{1}H-NMR spectra were obtained using a Jeol 90 MHz NMR spectrometer, a Varian XL-100 high-resolution NMR spectrometer, and a Varian EM-360 spectrometer (60 MHz).

1-(2-Hydroxy-5-methylphenyl)-2-phenyl-1-ethanone (8);[14] Modified Procedure:

4-Methoxyphenyl phenylacetate (22.6 g, 100 mmol) is dissolved in CS_2 (40 mL). Anhydrous $AlCl_3$ (22.6 g, 200 mmol) is added gradually. The rate of addition is so maintained that the solution is just boiling. After complete addition, CS_2 is distilled off, and the residue is heated at 130–140 °C for 3 h. The complex is broken by adding 5 N HCl (100 mL), at which point a red oil separates. The crude **8** is separated by steam distillation and purified by crystallization from aqueous EtOH; yield: 3.2 g (14%); mp 65–66 °C (Lit.[14] mp 65–66 °C).

The Mannich Reaction of 1-(2-Hydroxyphenyl)-1-ethanone, -1-propanone and -1-butanone and 1-(2-Hydroxy-5-methylphenyl)-2-phenyl-1-ethanone; General Procedure:

A secondary amine **9** (10 mmol) and formaldehyde (30% aq. solution, 2 mL) are dissolved in absolute EtOH (20 mL) saturated with dry HCl gas. The solution is warmed at ca. 60–70 °C for 15 minutes on a water bath. The appropriate ketone (10 mmol) is then added, and the solution is refluxed for 6 h. EtOH is distilled off, and the residue is dissolved in H_2O (15 mL). The aqueous layer is washed with ether (3 × 20 mL). The aqueous solution is made basic with aq. ammonia, thus giving the crude Mannich base, which is purified by column chromatography using silica gel. The elution is carried out with benzene/EtOAc (80:20, v/v). Its hydrochloride salt is prepared by passing dry HCl gas through its solution in absolute EtOH.

The characteristic data of compound **10–13** are recorded in Tables 1–4.

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