102. The Condensation of Cyclic Aminoketones, Cyclohexanone and Cyclohexane-1,4-dione with some Phenolic Ethers in Polyphosphoric Acid

by **Daniel Berney**

Wander Research Institute (a *Sandoz* Research Unit),
CH-3001 Berne, Switzerland

(6.XII.77)

Summary

The title condensations gave respectively: *gem*-bisarylated cyclic amines **3a–k** or monoarylated unsaturated cyclic amines **4a–g**, 1,3-bisarylated cyclohexadienes **6a**, **6b**, the condensed bicyclo[2,2,2]-octane **8**. In addition the aromatic ketone **9** gave the fluorenone **10** on treatment with polyphosphoric acid (PPA).

The condensation of two molecules of chlorobenzene with one molecule of *N*-methyl-4-piperidone in the presence of $AlCl_3$ to give 1-methyl-4,4-bis(4-chlorophenyl)-piperidine has been reported in the patent literature [1]. Another example of this type of reaction is the condensation of 2,6-dimethylphenol with 1-methyl-4-piperidone in HCl/AcOH which also gave a 4,4-bisarylated piperidine [2]. We report similar condensations *(Table)*[1]) of anisole (**1a**) and veratrole (**1b**) with cyclic aminoketones (**2a–f**) in PPA at 70°, where bisarylated cyclic amines **3a–k** were obtained *(Scheme 1)*.

When the condensation products of veratrole with cyclic aminoketones **3b**, **d**, **f**, **h** were heated in PPA at 120° for 20 min, one molecule of veratrole was lost to give the cyclic olefins **4a–d** *(Scheme 2)*. These olefins could also be obtained directly from veratrole and cyclic aminoketones by heating in PPA at 120° for 20 min.

When hydroquinone dimethyl ether (**1c**) was condensed with piperidone **2a** in PPA, two products were obtained: **4e** with an equimolar ratio of **1c** and **2a**, kept at RT. for 24 h, and **4f** with 1 equiv. of **1c** and 2.6 equiv. of **2a** at 60° in PPA for 24 h *(Scheme 3)*.

Equimolar amounts of 1,2,3-trimethoxybenzene (**1d**) and of piperidone **2a** stirred in PPA at RT. gave exclusively the olefinic product **4g** *(Scheme 4)*.

Attempts to prepare *gem*-bisarylcyclohexanes from cyclohexanone (**5**) and anisole or veratrole by this method failed; the only products isolated were 1,3-bisarylcyclohexa-1,3-dienes **6a**, **6b** *(Scheme 5)*.

The mechanism of this unusual reaction may be explained by the sequence presented in *Scheme 6*.

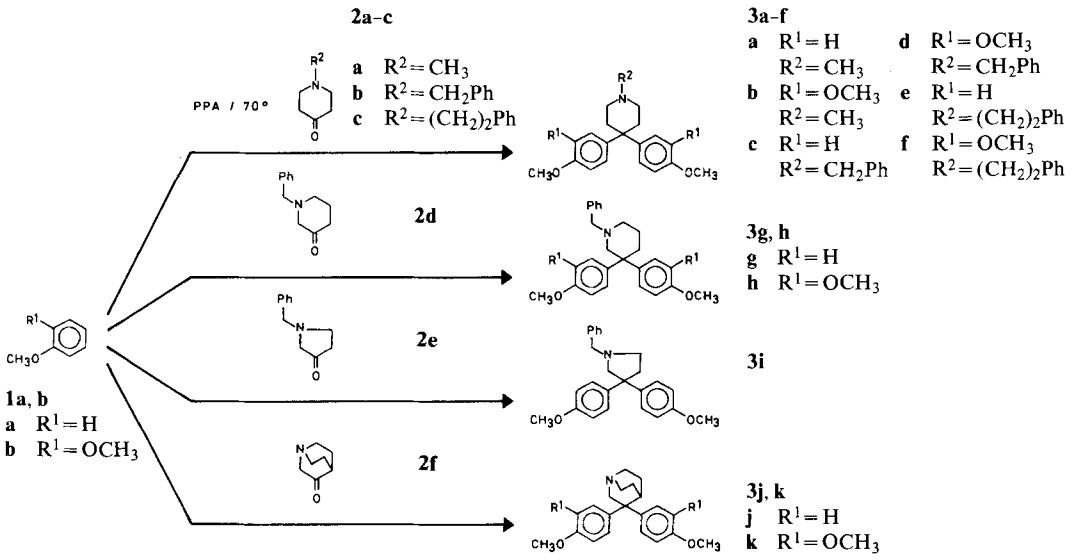
[1]) The *Table* summarizes all the experimental conditions.

Table

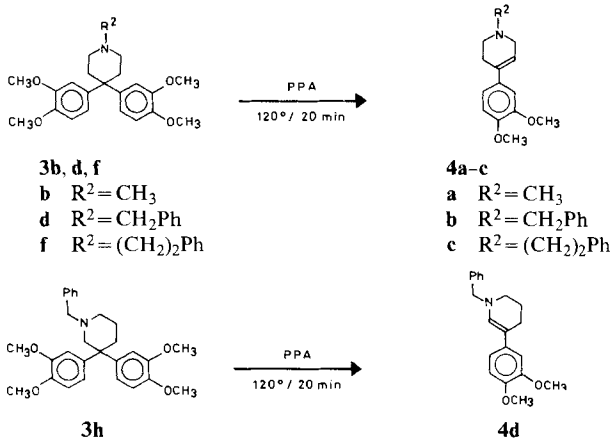
Product	Starting materials				Temp. °C	Time	Yield %	M.p. °C	Salt
	Ketone	equiv.	Arom. ether	equiv.					
3a	**2a**	1	**1a**	2.2	70	30 min	72[a])	276–279	NDS[d])
3b	**2a**	1	**1b**	2.2	70	30 min	70[a])	110–111	
3c	**2b**	1	**1a**	2.2	70	30 min	64[a])	295–299	NDS
3d	**2b**	1	**1b**	2.2	70	30 min	60[a])	217–221	HCl
3e	**2c**	1	**1a**	2.2	70	30 min	58[a])	283–285	NDS
3f	**2c**	1	**1b**	2.2	70	30 min	50[a])	215–219	HCl
3g	**2d**	1	**1a**	2.2	70	30 min	65[a])	> 300	NDS
3h	**2d**	1	**1b**	2.2	70	30 min	77[a])	192–199	HCl
3i	**2e**	1	**1a**	2.2	70	30 min	47[a])	212–215	HCl
3j	**2f**	1	**1a**	2.2	70	30 min	52[a])	165–166	
3k	**2f**	1	**1b**	2.2	70	30 min	75	267–270	HCl
4a			**3b**		120	20 min	22	216–221	NDS
4b			**3d**		120	20 min	23	278–281	NDS
4c			**3f**		120	20 min	26	> 310	NDS
4d			**3h**		120	20 min	55	oil	
4e	**2a**	1	**1c**	1	25	24 h	26	221–230	HCl
4f	**2a**	2.6	**1c**	1	60	24 h	40[b])	277–282	2 HCl
4g	**2a**	1	**1d**	1	25	6 h	70	195–200	HCl
6a	**5**	1	**1a**	1	25	72 h	43[b])	227–230	
6b[e])	**5**	1	**1b**	1	80	1.5 h	16[b])	137–140	
8	**7**	1	**1b**	2.1	25	16 h	82[c])	133–136	
10			**9**		120	4 h	30	119–120	

[a]) Based on the aminoketones. [b]) Based on the aromatic ether. [c]) Based on the diketone. [d]) Preparation of naphthalene-1,5-disulfonate (NDS) see [3]. [e]) Unstable.

Scheme 1



Scheme 2

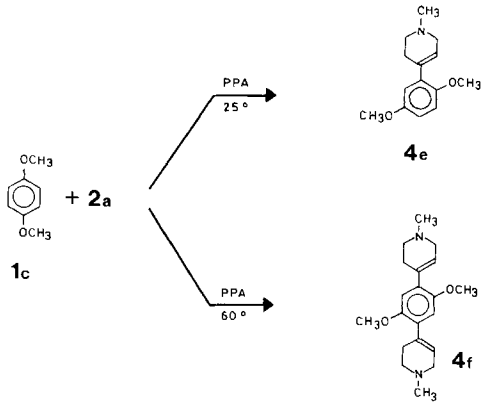


3b, d, f
b $R^2 = CH_3$
d $R^2 = CH_2Ph$
f $R^2 = (CH_2)_2Ph$

4a–c
a $R^2 = CH_3$
b $R^2 = CH_2Ph$
c $R^2 = (CH_2)_2Ph$

3h **4d**

Scheme 3



1c + **2a** → **4e**, **4f**

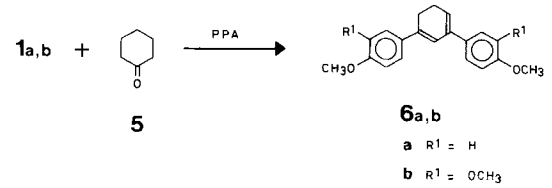
Scheme 4

1d + **2a** → **4g**

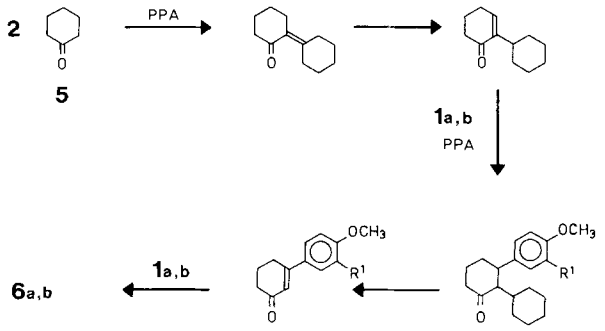
When 1 equiv. of cyclohexane-1,4-dione (**7**) was treated with 2.1 equiv. of veratrole (**1b**) in PPA at RT. the condensed bicyclo[2,2,2]-octane **8** was obtained *(Scheme 7)*.

Finally, we mention an unusual intramolecular condensation not directly related to the previous ones but also involving the reaction of an aromatic ether

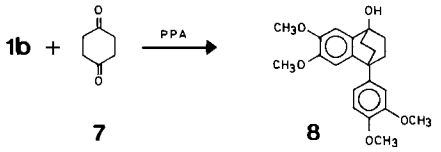
Scheme 5



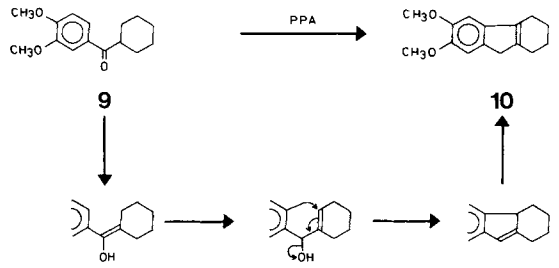
Scheme 6



Scheme 7



Scheme 8



with a carbonyl group, where both functional groups are on the same molecule. The aromatic ketone **9**[2]) was heated with PPA to give the indene **10**. The mechanism of this cyclization may be explained by the sequence presented in *Scheme 8*.

I thank *Th. Jauner* for his excellent experimental assistance.

[2]) The ketone **9** was prepared from veratrole and cyclohexane carboxylic acid in PPA at 100° for 30 min (m.p. 50–51°).

Experimental Part

General. NMR.-spectra were taken at 60 MHz in $CDCl_3$ with TMS as internal standard, using a *Varian* T-60 NMR. spectrometer. In the case of salts, a sample of the free base was prepared and used in $CDCl_3$. Abbreviations: *s* = singlet, *d* = doublet, *t* = triplet, *qa* = quadruplet, *m* = multiplet, br. = broad; chemical shifts in δ-values (ppm). All products (except compound **4d**) gave elemental analyses within $\pm 0.4\%$ of the theoretical values.

General procedure. – The cyclic ketone was thoroughly mixed with the phenolic ether and with about 10 parts by weight of PPA. The mixture was then heated at the temperature and for the time indicated in the *Table*. The hot solution was poured into ice-cooled water and extracted with $CHCl_3$ without previous alkalinisation in the case of compound **6a**, **b** and **8**. With *N*-containing products the acidic aqueous solution was made alkaline with 30% NaOH solution before being extracted with $CHCl_3$. The organic layer was washed with water, dried (Na_2SO_4) and evaporated to dryness. The salts were prepared by dissolving the oily residue in ethanol and adding a solution of the corresponding acid. Crystallization was aided by the addition of ether. Neutral compounds were crystallized from $CHCl_3$/petroleum ether.

Compounds **4a–d** were prepared by heating the solution of the bisarylated piperidines (free bases) **3b**, **d**, **f**, **h** in 10 parts of PPA; work-up as above. Compound **10** was obtained after heating the aromatic ketone **9** in 10 parts of PPA (see *Table*).

NMR. data. – *4,4-Bis(4-methoxyphenyl)-1-methylpiperidine* (**3a**). 7.0 (2 *d*, 8 H arom.); 3.8 (*s*, 2 CH_3O).

4-(2,3-Dimethoxyphenyl)-1-methyl-1,2,5,6-tetrahydropyridine (**4a**). 6.1 (*t*, H–C(3)); 4.0 (2 *s*, 2CH_3O); 3.2 (*m*, 2 H–C(2)); 2.4 (*s*, CH_3N).

1-Benzyl-5-(2,3-dimethoxyphenyl)-1,2,3,4-tetrahydropyridine (**4d**). 7.3 and 6.3 (2 *s*, (3+5) H arom.); 6.5 (*s*, H–C(6)); 4.1 (*s*, NCH_2Ph); 3.8 (2 *s*, 2 CH_3O); 2.8 and 2.4 (2 *t*, 2 H–C(4) and 2 H–C(6)); 2.0 (*qa*, 2 H–C(3)).

2,5-Dimethoxy-1,4-bis[1-methyl-1,2,5,6-tetrahydro-4-pyridyl]benzene (**4f**). 6.7 (*s*, 2 H arom.); 5.8 (*t*, 2 H–C(2)–C(2′)); 3.7 (*s*, 2 CH_3O); 3.0 (*m*, 4 H–C(1)–C(1′)); 2.6 (*s*, 2 CH_2CH_2); 2.3 (*s*, 2 CH_3N).

1,3-Bis(4-methoxyphenyl)cyclohexa-1,3-diene (**6a**). 7.6, 6.9 (*m*, 8 H arom.); 6.5 (*s*, H–C(2)); 6.0 (*m*, H–C(4)); 3.8 (*s*, 2 CH_3O); 2.5 (*m*, 2 H–C(5) and 2 H–C(6)).

6,7-Dimethoxy-4-(3,4-dimethoxyphenyl)-1,4-ethano-1,2,3,4-tetrahydro-1-naphthalol (**8**). 7.2, 7.0 and 6.3 (3 *s*, 5 H arom.); ~ 3.8 (3 *s*, 4 CH_3O); 2.4 (*s*, HO); 2.0 (br. *m*, 2 CH_2CH_2).

6,7-Dimethoxy-1,2,3,4-tetrahydro-9H-fluorene (**10**). 7.0 and 6.9 (2 *s*, 2 H arom.);3.95 and 3.9 (2 *s*, 2 CH_3O); 3.2 (br. *s*, 2 H–C(9)); 2.4 (*m*, 2 H–C(1) and 2 H–C(4)); 1.8 (*m*, 2 H–C(2) and 2 H–C(3)).

REFERENCES

[1] *G. Hackmack, H.G. Menge & J. Klosa,* Ger. Offen. 2.139.085; Chem. Abstr. *78*, 124456 h (1973).

[2] *S.M. McElvain & R.S. Berger,* J. Amer. chem. Soc. *77*, 2848 (1955).

[3] *D. Berney & K. Schuh,* Helv. *58*, 2228 (1975).