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AMINOMERCURATION XIV. A NOVEL SYNTHETIC ROUTE TO AMINO-ALCOHOLS

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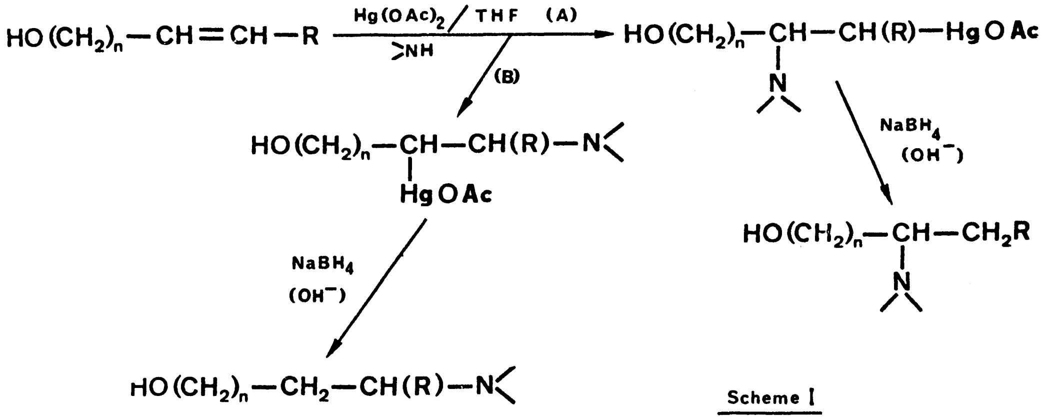
Olefins carrying a proximate hydroxyl group undergo efficient aminomercuration, thus affording aminoalcohols. In some cases this synthesis is of particular interest owing to the known therapeutic activity of the products.

The early limitations to the aminomercuration reaction with olefins, which arise from mercuric salt complexation,[1)] have been partially overcome by adding water to the reaction mixture. There is no interference from the oxymercuration process.[2)]

It is well known that mercuric salts and amines form very stable complexes which inhibit double bond mercuration and further attack by the amino group. We now observe that addition of another soft ligand to the reaction mixture renders, at least in some cases, the reaction possible; if this extra ligand is attached to the double bond chain, the reaction affords functionalized aminomercuric compounds.

In all cases the only observed reaction is double bond amination and never intramolecular oxymercuration.

We present here examples which show the effect of proximate ligand on the reaction of aminomercuration.



Scheme I

The reaction has proved to be general in the cases so far investigated of aromatic amines, affording amino-alcohols with satisfactory yields, and this is independent of the chain-length, the double-bond (cyclic or acyclic starting material), and the strain of the ring in which the double-bond is included.

We first checked that the hydroxyl group is required for amination to occur, as is the case for water in the previously investigated reactions;[3)] thus, 1-butene amination by the couple $Hg(OAc)_2$

/aniline is only achieved if water is present, while 3-buten-1-ol (cf. 2 in the table)undergoes amination without water and leads to the amino-alcohol with a good yield; this result demonstrates for the first time, the involvement of an oxygen atom in a coordinated transition state in the process of mercuration at a double bond.4)

Other results are summarized in the table 1.

Several comments may be made :

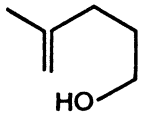
a) - A single reaction is observed, intermolecular amination of the double-bond being the only process; notably ring closure by intramolecular mercuration of the ethylenic alcohol5,6) does not compete with amination.

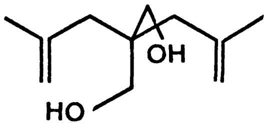
b) - The reaction is regiospecific. This result is also related to the intramolecular oxygen coordination (amination of 7), since it is well known7,8)that mercuration of alkyl substituted cyclohexenes leads to a mixture of isomers.

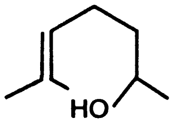
c) - Amination of 3 leads to a mixture of monoaminated compound 4 and its cyclized product; cyclisation of 4 after isolation can be completed. This particular example shows the potential utility of this reaction in alkaloïd chemistry.

d) - Reaction with 8 was carried out with the endo-exo mixture (70/30); only the endo isomer reacted.

e) - The only limitation observed was concerned with gemm disubstituted double-bond. The three following compounds :





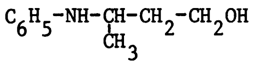
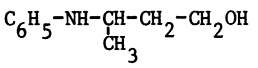
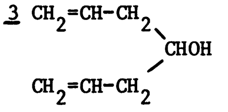
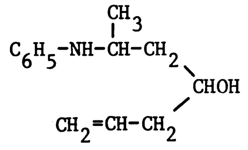
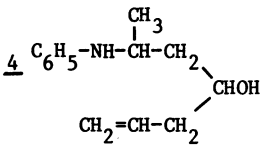
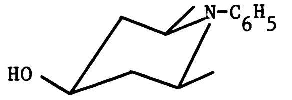
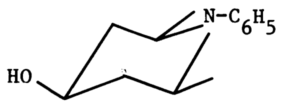
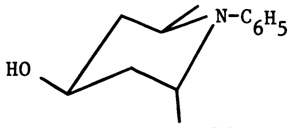
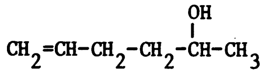
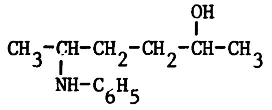
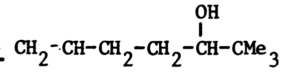
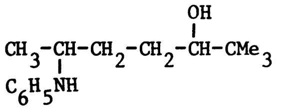
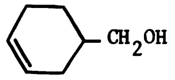
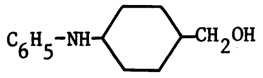
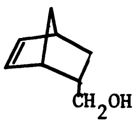
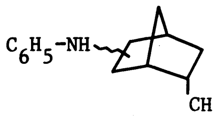


cannot be aminated by this process; the products result from cyclisation leading to oxygenated cycles.

Amination of 2

To a suspension of 20 mmol (6.34 g) of $Hg(OAc)_2$ in 40 ml of THF, 0.06 mol (5.58 g) of freshly purified aniline in 5 ml THF was added. A white heavy precipitate was formed after a few minutes. 20 mmol (1.44 g) of 3-buten-1-ol in 10 ml THF was then added : the solution became clear after 15 minutes; after another 15 minutes, the solution was cooled down and neutralized by adding 25 ml of 1N NaOH before demercuration (15 mmol $NaBH_4$ in 10 ml 1N NaOH).

THF was then evaporated, and the aqueous layer was saturated with NaCl before extraction with Et_2O. Distillation affords 2.24 g (68%) of amino-alcohol purified (from starting materials) by preparative glc (Carbowax, 20M, 200°C, flow rate 2.5 ml/sec; retention time 2.5 hours).

N°	Starting Ethylenic Alcohols	Amino-alcohols	Yields %	NMR ppm/TMS	IR(neat) cm^{-1}
1	$CH_3-CH=CH-CH_2OH$	 $C_6H_5-NH-\underset{CH_3}{CH}-CH_2-CH_2OH$	52	(CCl$_4$)6.5-7.3,m,5H,phenyl;3.7,t,2H (CH$_2$O)J=6Hz;3.6,q,1H(CHN)J=6Hz;3.2,m, 2H(NH,OH);1.7,2t,2H,J=6Hz;1.2,d,3H, J=6Hz.	ν_{OH}3550 ν_{NH}3360
2	$CH_2=CH-CH_2-CH_2OH$	 $C_6H_5-NH-\underset{CH_3}{CH}-CH_2-CH_2OH$	68	ibid.exept(NH,OH) at 3.4	ibid.
3			63	(CDCl$_3$)6.5-7.3,m,5H,phenyl;5.4-6.2,m, 1H,vinyl,4.8-5.3,m,2H,vinyl,3.4-4,m, 2H,(CHO,CHN);3.3,m,2H,(NH,OH);2.2,t, 2H,J=6Hz;1.5,t,2H,J=6Hz;1.1,d,3H, J=6Hz.	ν_{OH}3540 ν_{NH}3380 $\nu_{C=C}$1640
4		 +	7	(CCl$_4$)7.2,5H,phenyl;3.5-4,m,2H,(CHO, OH),2.6-3.2,m,2H,(CHN);1-2.2,m,4H, (CH$_2$);0.85,d,6H,J=6Hz.	ν_{OH}3340 ν_{C-OH}1040 (OH eq)
			51	ibid.	ibid.
			6	(CCl$_4$)6.8-7.3,m,5H,phenyl;3.1-4.2, m,3H(CHO,CHN);2.7-2.9,1H,(OH);1.1-2.3,m,4H,(CH$_2$);1,d,3H,J=6Hz.	IR(Nujol) ν_{OH}3240, 3310 ν_{C-OH}1025 (OH eq)
5	 $CH_2=CH-CH_2-CH_2-\overset{OH}{CH}-CH_3$	 $CH_3-\underset{NH-C_6H_5}{CH}-CH_2-CH_2-\overset{OH}{CH}-CH_3$	35	(CCl$_4$)6.4-7.3,m,5H,phenyl;3.3-4,m, 2H,(CHO,CHN);2.8,s,2H,(OH,NH);1.4-1.6,m,4H;1.1,d,6H,J=6Hz.	ν_{OH}3540 ν_{NH}3380
6	 $CH_2-CH-CH_2-CH_2-\overset{OH}{CH}-CMe_3$	 $CH_3-\underset{C_6H_5NH}{CH}-CH_2-CH_2-\overset{OH}{CH}-CMe_3$	30	(CDCl$_3$)6.4-7.3,m,5H,phenyl;3-3.7,m, 2H,(CHO,CHN);2.5,s,2H,(OH,NH);1.3-2.1,m,4H;1.2,d,3H,J=6Hz;0.8,s,9H (tBu).	ν_{OH}3570 ν_{NH}3390
7			57	(Pyridine-d$_5$)6.5-7.6,m,5H,phenyl; 5.4,s,2H,(NH,OH);3.4-3.8,m,3H, (CH$_2$O,CHN);1.3-2.2,m,9H.	ν_{OH}3540 ν_{NH}3380
8		 ++	30	(CDCl$_3$)6.4-7.3,m,5H,phenyl;3.1-3.5, m,3H(CH$_2$O,CHN);2.4-2.6,m,2H,(OH,NH); 1-2.4,m,9H(CHand CH$_2$ of the cycle).	ν_{OH}3550 ν_{NH}3390

+Configuration for the cyclisation products of 4 have been assigned on the basis of previous determinations in piperidine derivatives[9)] and checked elsewhere[10)] for the position of methyl group, according to G. Chiurdoglu[11)] for the OH group position.

++Position of the amino group and relative configurations are being elucidated.

References

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