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HYDROGENOLYSIS OF BENZYLAMINE DERIVATIVES

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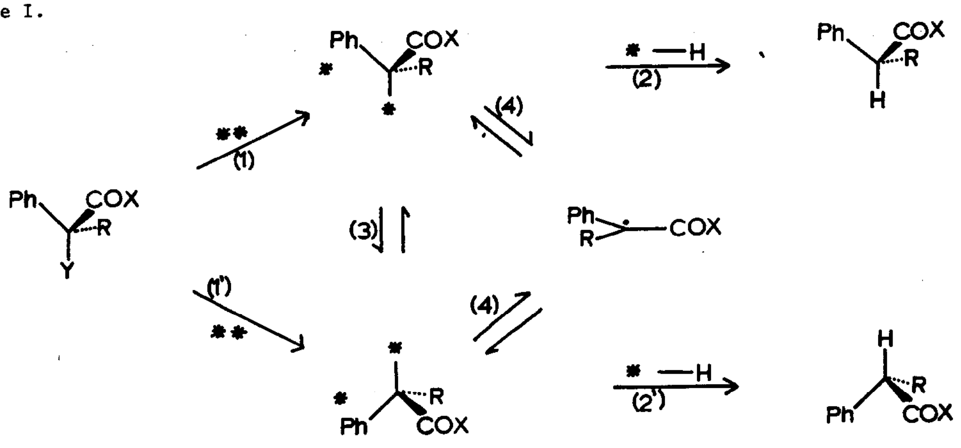
Recent work by Mitsui and Sugi$^{1)}$ on the stereospecific hydrogenolysis of benzylamine derivatives prompts us to report our findings in this field. Compounds of type I have been prepared in optically active form and their absolute stereochemistry determined$^{2)}$.

I II

Y = some nitrogen containing functional group

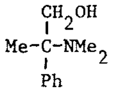
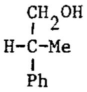
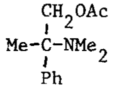
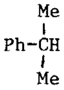
The results of the hydrogenolyses of these substrates are summarised in Table I. All these reactions with the exception of experiments 3 and 16, proceed with high stereospecificity. They are in accord with the general result that palladium favours inversion of configuration in all types of benzylic substituent hydrogenolysis.

The results may be accounted for by a qualitative and general mechanism and which is consistent with the findings of Mitsui and Coworkers$^{1)}$. The mechanism is outlined in Scheme I.



Scheme I

TABLE I. Stereochemistry of hydrogenolyses with 10% palladium on charcoal

Exp.	Substrate I Y	 X	Product II X	Optical purity	Reaction Stereospecificity	Reference
1	NH_2	OH	Starter	-	-	2c
2	NH_2	OMe	"	-	-	2c
3	NH_2	OEt[b]	OEt	7%	53.5% retention of configuration	3
4	NH.CHO	OH	Starter	-	-	2c
5	NH.CHO	OMe	"	-	-	3
6	NHAc	OEt	"	-	-	2c
7	NHPh	OH	OH	52%	76% inversion of configuration[c]	4
8	NHPh	OH	OH	22-67%	61-83% inversion of configuration[d]	3
9	NHPh	OMe	OMe	30-70%	65-85% inversion of configuration[d]	3
10	NMe_2	OH	OH	94-96%	97-98% inversion of configuration[e]	2b, this work
11	NMe_2	OH[f]	OH	90%	95% inversion of configuration	this work
12	NMe_2	OMe	OMe	45%	72% inversion of configuration	2b
13	NMe_2	OEt	OEt	59%	79% inversion of configuration	2c
14	NMe_2	OEt	OEt[g]	73%	86% inversion of configuration	this work
15	NMe_2	NH_2	NH_2	67%	84% inversion of configuration	2c
16	$\overset{+}{N}Me_3\overset{-}{I}$	OMe	OMe	0%	racemisation	2b
17	 $\mathrm{Me{-}\overset{\overset{CH_2OH}{\vert}}{\underset{\underset{Ph}{\vert}}{C}}{-}NMe_2}$		 $\mathrm{H{-}\overset{\overset{CH_2OH}{\vert}}{\underset{\underset{Ph}{\vert}}{C}}{-}Me}$	97.5%	99% inversion	this work
18	 $\mathrm{Me{-}\overset{\overset{CH_2OAc}{\vert}}{\underset{\underset{Ph}{\vert}}{C}}{-}NMe_2}$		 $\mathrm{Ph{-}\overset{\overset{Me}{\vert}}{\underset{\underset{Me}{\vert}}{CH}}}$	-	-	this work

a) Moles of catalyst per mole substrate was 1:18 approximately. Solvent was ethanol except where solubility problems demanded the use of water or EtOH-water mixtures.

b) 150°C and 60 atm. pres. There was no reaction at room temperature and pressure[2c].

c) Assuming that the optical purity of this substrate given in reference 3 is 100%.

d) The authors state there was retention of configuration. However latter work shows[2c] that they had incorrectly assigned the configuration of the substrate.

e) With palladium metal there is 99% inversion of configuration.

f) 1 equivalent of triethylamine added. g) 1 equivalent of acetic acid added.

The first step in the hydrogenolysis of these benzylic derivatives is the formation of π-benzyl complexes via different transition states depending on the catalyst metal[5] and substituent Y. Steps 1 and 1' may be occurring competitively but the relative rates of these processes are such as to lead predominantly to only one enantiomeric complex depending on the catalyst and/or substituent Y.

Pathways by which racemisation can conceivably occur are steps 3 and 4. Equilibrium 3 could take place by a rollover mechanism or by attack by another atom (or atoms) of catalyst on the complex at a step[6] on the catalyst surface. Step 4 is a racemisation process which probably occurs extensively when the substrate contains a group capable of poisoning the catalyst. Halides and sulfides are known catalyst poisons and by partially or totally deactivating the catalyst (presumably by hydrogen desorption) slow down or stop steps 2 or 2' leading to hydrogenolysis product. In addition deactivation favours radical desorption with concommitant racemisation.

Stereospecific hydrogenolyses with inversion of configuration (expts. 7-15,17) is considered to proceed to complex formation predominantly via step 1' which may or may not equilibrate via steps 3 and 4 depending on the various groups attached to the asymmetric carbon atom. Hydrogenolysis is accomplished via step 2'.

In the hydrogenolysis of quaternary ammonium iodide (expt 16) partial deactivation of the catalyst by iodide upon step 1 or 1' leads to desorption of hydrogen which slows down steps 2 and 2' and allows equilibrium 4 to be reached. Thus racemisation is observed.

Stereospecific hydrogenolysis with retention of configuration (expt 3) is suggested to proceed via steps 1 and 2 with serious divergence through equilibria 3 and 4. Why the hydrogenolysis with palladium takes this route in this case is not clear. It is interesting to note that while all the other hydrogenolyses were performed at room temperature and pressure, this one could take place only at elevated temperature and pressure. It is also worthy of note that the ease of amine debenzylation at room temperature and pressure increases[7] in the series primary < secondary < tertiary amine< quaternary ammonium hydroxide while at conditions comparable to those in which expt. 3 was run this order is reversed[8]. These results also suggest that hydrogenolysis proceeds via different pathways under the different conditions.

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