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"OXAZOLIDINES. A CASE OF EASY DEHYDROGENATION"

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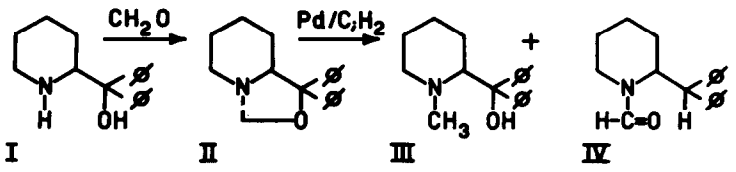
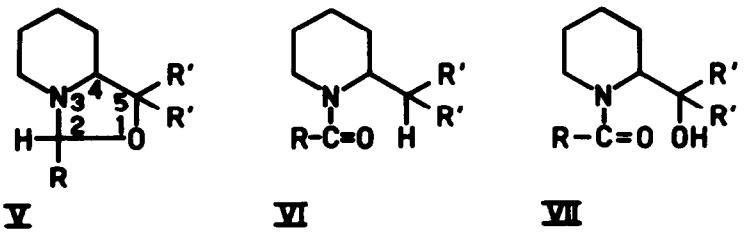
Alkylation of 1,2-aminoalcohols is usually performed in high yields by condensation of the aminoalcohol with the appropriate aldehyde followed by catalytic hydrogenation of the resulting oxazolidine (1).

When we applied this procedure to the synthesis of III, substantial (20 %) quantities of a neutral by-product IV were isolated, beside the expected III (2). Compound IV was found to be an isomer of the oxazolidine II; the IR spectrum showed the presence of an amide band and the absence of either O-H and C-O- bands, the NMR spectrum presented a singlet at 7.75 δ (formyl proton) and therefore on these grounds we assigned to IV the structure of diphenyl-2-(N-formyl)-piperidylmethane.



The formation of IV was next investigated and it was found that, among all variables, the catalyst was the important one : by refluxing in absence of hydrogen an ethanol solution of II with a 25 % by weight of 5 % palladized carbon or Raney nickel compound IV was secured in over 90 % yield, whereas in absence of the catalyst no reaction occurred even in presence of strong acids or bases.

To gain some insight on the reaction mechanism a group of oxazolidines (see table I) of general formula V were subjected to the same treatment (4).



Quite unexpectedly we found that two different kinds of neutral products were formed, either the amides VI or the hydroxyamides VII, moreover the reaction was clear-cut giving either VI or VII but not a mixture of both (5). When the hydroxyamides were isolated, a corresponding amount of hydrogen was also liberated (plus a small amount of CO and CH_4); when the amides VI were formed, only about 4 % of hydrogen (including some CH_4) was collected. The reaction path was found to be strongly dependent on the nature of the C_5 substituent (R'), whereas R seemed to effect only, and to a small extent, the reaction rate.

The 5,5-diphenyloxazolidines (formula V, R' = C_6H_5; compds. N° 1, 2, 3) gave within two hours the amides VI (N° 7, 8, and 9) in almost quantitative yield. The hydroxyamides VII, however, are not an intermediate (8).

The 5,5-dimethyloxazolidines (formula V, R' = CH_3; compds. N° 4, 5) reacted much slower : after 24 hours much starting material was recovered unchanged and the hydroxyamides VII (N° 10 and 11) were isolated in about 40 % yield. The structure of the amides was deduced from the IR and NMR spectra and it was confirmed by synthesis (Schotten-Baumann acylation of dimethyl-2-piperidylcarbinol).

TABLE I

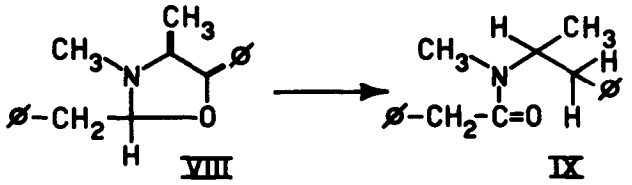
N°	Compd.	R	R'	m. p. (6)
1	V	H	C_6H_5	123° (7) (.MeI m.p. 130°)
2	V	$C_6H_5CH_2$	C_6H_5	113° (.$MeClO_4$ m.p. 286° dec.)
3	V	C_6H_4OH(p)	C_6H_5	60°
4	V	C_6H_5	CH_3	Oil (.HCl m.p. 194°)
5	V	$C_6H_5CH_2$	CH_3	Oil (.HCl m.p. 196°)
6	V	$C_6H_5CH_2$	H	62°
7	VI	H	C_6H_5	157°
8	VI	$C_6H_5CH_2$	C_6H_5	165°
9	VI	C_6H_4OH(p)	C_6H_5	247°
10	VII	C_6H_5	CH_3	99°
11	VII	$C_6H_5CH_2$	CH_3	83°
12	VII	$C_6H_5CH_2$	H	98°

In the case of the unsubstituted oxazolidine (compd. N° 6) the reaction was also slow : the hydroxyamide VII (N° 12), whose structure was confirmed by synthesis, was isolated in 45 % yield. Moreover we were able to recover, beside some starting material, ethyl phenylacetate in about 15 % yield. Some 2-piperidylcarbinol was also found to be present by TLC.

Further investigation showed that :

1°) When the nitrogen lone pair of electrons is no longer free as in a quaternary salt, e.g. 3H-1,1-diphenyl-3-benzyl-4-methyl-hexahydrooxazolo [3,4-a] piperidinium perchlorate (see compd. 2) (9), the reaction is completely suppressed and the salt is recovered unchanged.

2°) Condensation between l-ephedrine and phenylacetaldehyde gave the oxazolidine VIII (m. p. 80°), which by treatment with Pd on carbon afforded the amide IX (80 % yield, b.p. 145° at 0.3 mm Hg-$[\alpha]_D^{20}$ + 49°). The same amide (identical IR spectrum, $[\alpha]_D^{20}$ + 47°) was obtained by treating l-desoxyphedrine (10) with phenacetyl chloride.

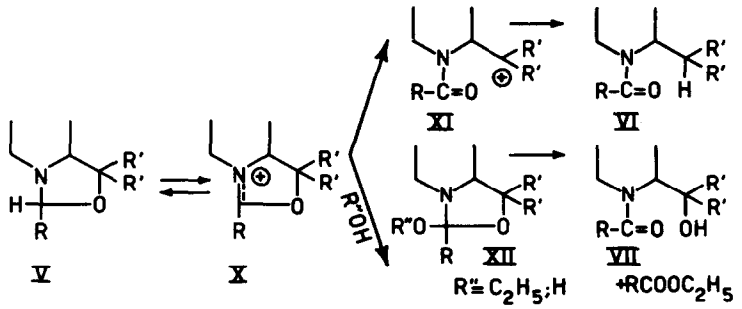


VIII IX

This result suggest that the presence in the oxazolidine of a single C_5 phenyl group is probably sufficient to direct the reaction toward the formation of the amide rather than the hydroxyamide. Moreover the optical purity of IX shows that C_4 is not involved in the reaction.

3°) Attemps to obtain the hydroxyamide VII instead of the amide VI by adding a hydrogen scavenger were unsuccessful. No hydroxyamide VII was detected when compd. 2 was refluxed in ethanol in the presence of Pd on carbon and either cyclohexene or nitrobenzene.

To explain the results we have reported, which are quite uncommon since catalytic dehydrogenations are usually performed at much higher temperature (11), we suggest the following tentative mechanism :



V X XI VI XII VII

R"≡ C_2H_5;H +$RCOOC_2H_5$

Abstraction of a hydride ion gives a higly stabilized ion X : when R' = C_6H_5, X rearranges to the resonance stabilized carbonium ion XI, which by hydride attack affords the amide VI (12, 13). When R' = CH_3 or H, the carbonium ion XI would be poorly stabilized and is therefore improbable : nucleophilic addition to X affords the ortho-amide XII which subsequently gives the hydroxyamide VII and eventually the ester R-COOOC_2H_5 (14).

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REFERENCES

1) E.D. Bergman, Chem. Rev., 53, 318 (1953).

2) As far as we know, there is only one previous report (3) about the concurrent formation of neutral substances during the catalytic hydrogenation of equimolar amounts of aminoalcohols and aldehydes. However the structure of these by-products was not investigated.

3) A.C. Cope and E.M. Hancock, J. Am. Chem. Soc., 64, 1503 (1942).

4) Samples were taken at regular intervals and examined by TLC : in this way a rough estimate of the reaction rate was obtained.

5) Owing to experimental uncertainties we cannot exclude the formation of a minor component up to about 10 %.

6) All the compounds gave satisfactory elemental analysis.

7) F.J. McCarty, C.H. Tilford, and M.G. Van Campen, J. Am. Chem. Soc., 79, 472 (1957).

8) The hydroxyamide VII (R' = C_6H_5; R = $C_6H_5CH_2$; m.p. 132°) was treated with an equal weight of Pd on carbon in boiling ethanol for several hours : the product was recovered unchanged und no desoxyamide VI could be detected.

9) A perchlorate, instead of the iodide, was used because we found that this anion is without ill effects on the catalyst, whereas the iodide anion poisons it.

10) Ming-Chien Chiang, J. Chinese Chem. Soc., 17, 106 (1950). C.A., 47, 9293 (1953).

11) L.M. Jackman. Advances in Organic Chemistry, 2, p. 352. Interscience, New York (1960).

12) The higher reaction rate when R' = C_6H_5 and the results of point 3°) suggest a concerted intramolecular hydride transfer. To set this point we are currently investigating the stereochemistry of this reaction.

13) The reaction could also be initiated by a hydrogen atom abstraction, leaving a stabilized radical. We can however exclude a radical chain mechanism, because the formation of VI is neither inhibited by hydroquinone nor, in absence of the catalyst, could be induced by benzoyl peroxide.

14) The reaction could conceivably be initiated by a hydride attack. However the oxazolidine N° 7 was recovered unchanged when refluxed in benzene in the presence of NaH.