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A RE-INVESTIGATION OF THE ACID-CATALYZED CYCLIZATION OF δ-HYDROXYAMIDES

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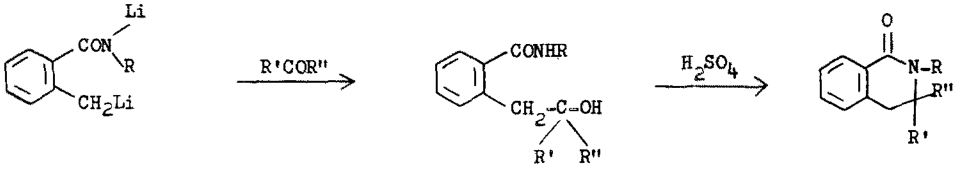
During an investigation involving the synthesis of various isoquinoline derivatives we had cause to use the procedure of Hauser et. al. (1) to prepare intermediate dihydroisocarbostyrils beginning with IIIa.



I II III

a. $R = \emptyset CH_2$, $R' = R'' = CH_3$

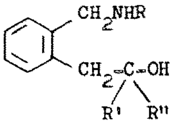
b. $R = CH_3$, $R' = R'' = C_2H_5$

c. $R = CH_3$, $R' = \emptyset$, $R'' = H$

d. $R = CH_3$, $R' = \emptyset$, $R'' = C_2H_5$

e. $R = CH_3$, $R' = R'' = \emptyset$

Surprisingly, IIIa was resistant to LAH reduction in various solvents and was only reduced with LAH-$AlCl_3$ in boiling ether-THF. The product was a crystalline amino alcohol, m.p. 75-7°, IR_{CHCl_3} 3300, 3140 cm^{-1}; identical in all respects (NMR, IR, mass spec. M^+ 269) with the LAH-$AlCl_3$ reduction product of IIa, and thus formulated as IVa. A plausible explanation

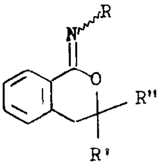


IV

a. $R = \emptyset CH_2$, $R' = R'' = CH_3$

b. $R = CH_3$, $R' = R'' = C_2H_5$

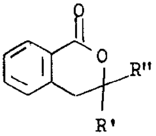
for this unexpected product was that the acid cyclization step (II→III) had proceeded instead to give Va.



V

a. R = ØCH_2, R' = R" = CH_3
b. R = CH_3, R' = R" = C_2H_5
c. R = CH_3, R' = Ø, R" = H
d. R = CH_3, R' = Ø, R" = C_2H_5
e. R = CH_3, R' = R" = Ø

Re-examination of the IR spectrum of the acid cyclization product revealed strong bands at 1120 and 1090 cm^{-1} (ether) consistent with structure V. Further confirmation was obtained by the acid hydrolysis (refluxing 3N HCl) of Va to give the lactone VIa, also obtained by thermal cyclodeamination of IIa (2).



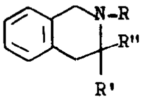
VI

a. R' = R" = CH_3
b. R' = R" = C_2H_5
c. R' = Ø , R" = H
d. R' = Ø, R" = C_2H_5

Since the Hauser reaction sequence was important to our work we re-examined four representative δ-hydroxyamides (II b-e) described by these authors. From the reaction of the hydroxyamides with cold conc. H_2SO_4, we isolated the following cyclization products:

δ-Hydroxyamide	3,4-Dihydroisocarbostyril	Imino Ether
IIb	IIIb (0%)	Vb (82%)
IIc	IIIc (8%)	Vc (92%)
IId	IIId (7%)	Vd (93%)
IIe	IIIe (43%)	Ve (51%)

When IIe was refluxed in gl. HOAc with a catalytic amount of H_2SO_4, IIIe, m.p. 198-9° [reported m.p. (1) 196-8°] was obtained in 87% yield. Each of the imino ether structures was supported by IR, (C = N 1645-1655 cm^{-1}, OR, 1115-1120 and 1090 cm^{-1}), NMR and mass spec. and by hydrolysis to the corresponding lactones whose structures were, in turn supported by physical measurements. Authentic samples of IIIb and c (m.p. 53-4° and 118-9° respectively) were obtained by PPA cyclization of $C_6H_5CH_2C(R')(R'')NCO$ followed by NaH catalyzed alkylation with CH_3I. Reduction of IIIb (with LAH-$AlCl_3$) and IIIe (with LAH) gave VIIa and b, respectively while reduction of Vb gave IVb. Attempted hydrolysis of IIIb

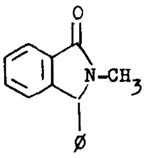


a. $R = CH_3$, $R' = R'' = C_2H_5$

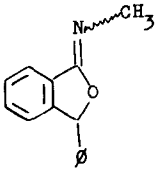
b. $R = CH_3$, $R' = R'' = Ø$

VII

(refluxing 3N HCl) resulted in the quantitative recovery of starting material. Of the compounds re-examined, only the 3,3-diphenyl structure IIIe of Hauser et. al. appears correct. Furthermore, in a subsequent publication (3) paralleling the above and dealing with lower-ring homologs, one alleged phthalimidine VIII, has been shown in our re-investigation to be the isomeric imino ether IX. Proof of the structure was accomplished by hydrolysis to 3-phenylphthalide and by comparison with authentic VIII, (m.p. 101-102.5°) (4), prepared by catalytic hydrogenolysis of 3-hydroxy-2-methyl-3-phenylphthalimidine (5). Attempted acid hydrolysis of VIII returned 90% of the starting material.



VIII



IX

Caution should therefore be exercised in the interpretation of the data contained in these two papers. A publication dealing with the complete clarification of the dihydroisocarbostyril case and a restatement of mechanism will be published in the near future in J. Het. Chem.

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3) C. Mao, I. T. Barnish and C. R. Hauser, J. Het. Chem. 6, 475 (1969).

4) Which agrees with the previously published m.p. of 105°, W. Theilacker and W. Schmidt, Ann., 597, 95 (1955).

5) G. Wittig, G. Closs and F. Mindermann, ibid, 594, 89 (1955).