New Transformations in the 1,4-Dihydropyridine Series

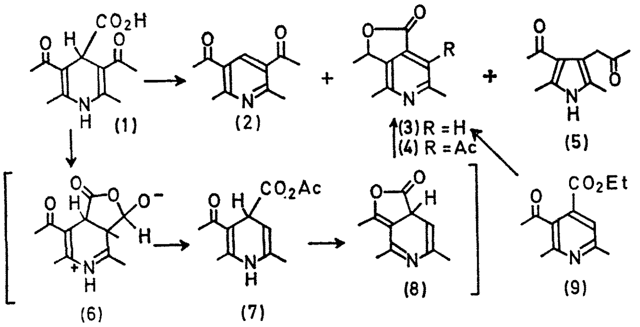
By J. F. BIELLMANN,* R. J. HIGHET,† and M. P. GOELDNER

(*Laboratoire associé au CNRS, Institut de Chimie, rue B. Pascal, 67-Strasbourg, France and †National Heart and Lung Institute, Bethesda, Maryland, U.S.A.*)

Summary The dihydropyridine acid (**1**) is transformed by pyrolysis mainly into the lactone (**3**) whereas the acid (**10**) is transformed into pyridines (**11**), (**12**), (**13**), (**14**), and (**15**).

IN our continuing study of the properties of 1,4-dihydropyridine-4-carboxylic acids[1,2] we have prepared and heated the acids (**1**) and (**10**). The former material was formed by the Hantzsch condensation[3] of the imine of acetylacetone and glyoxylic acid in ethanol, (**1**) being obtained pure by chromatography on silicic acid.

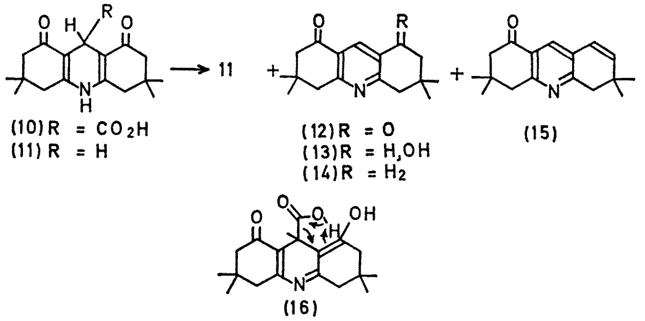
Heating (**1**) at 240° produced a mixture of three products: the known pyridine (**2**)[4] in trace quantity, the lactone (**3**) (88%), and the pyrrole (**5**) (8%). The structure of (**3**) was demonstrated by its preparation from the ketonic ester (**9**)[5] by reduction with sodium borohydride; lactone formation followed the reduction spontaneously. Identification of the pyrrole (**5**) was achieved by its preparation from 2,5-dimethyl-3-acetylpyrrole[6] by addition of the carbene from diazoacetone.[7]



The acid (**1**) behaved similarly in refluxing solvents. For instance, refluxing 1·5 hr., in diglyme transformed (**1**) into (**2**) (7%), (**3**) (37%) and (**5**) (43%); refluxing 1 hr. in ethylene glycol produced (**2**) (8·5%) and (**3**) (78%). Protonated solvents favour the formation of the lactone (**3**) at the expense of the pyrrole (**5**). In the course of the pyrolysis, a quantity of acetic acid is liberated corresponding to that of the lactone (**3**).

We suggest that the first step in the pyrolysis of the acid (**1**) is protonation at C-3 of the pyridine, followed by addition of the carboxyl to the ketone to form (**6**), which fragments to form the mixed anhydride (**7**). Transformation into the lactone (**8**) with liberation of acetic acid and subsequent acid-catalysed double-bond shift provide the lactone (**3**). A transformation of the type of (**7**) → (**3**) is, indeed, produced by treatment of the acid (**1**) by acetic anhydride at room temperature, the lactone (**4**) being isolated in more than 80% yield. Identical material could be prepared from the methyl ester of (**1**) by oxidation to the corresponding pyridine ester by sodium nitrite in acetic acid and subsequent reduction by sodium borohydride.

Heating the dimedone derivative of glyoxylic acid in a sealed tube with an ethanolic solution of ammonia (85°, 24 hr.) precipitated the ammonium salt of (**10**), the free acid was readily obtained by acidification. Heating (**10**), at 280° transformed it into at least five major products: (**11**) (10%), (**12**) (24%), (**13**) (38%), (**14**) (14%), and (**15**) (15%). The structure of (**11**) and (**12**) were demonstrated by comparison with authentic materials.[8] The keto-alcohol (**13**) could be oxidized to (**12**) by manganese dioxide. The structure of (**14**) and (**15**) are based on spectroscopic observations.



The presence of the polycyclic system of the acid (**10**) prevents the reaction course observed in the case of the monocyclic (**1**). It would appear that the alcohol (**13**) can be formed by decarboxylation of the enol, as shown in (**16**), the other aromatic products arising from (**13**). Refluxing (**10**) in triglyme for one hour does, indeed, produce predominantly (**13**), which, heated alone at 280°, produces a mixture of (**12**), (**14**), and (**15**) besides unchanged (**13**). The non-aromatic product (**11**) apparently arises from simple decarboxylation of $\beta\gamma$-unsaturated acid followed by acid isomerisation.

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