Ring Contraction in the 1,4-Dihydropyridine Series

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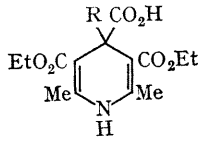
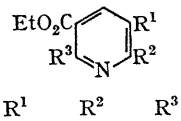
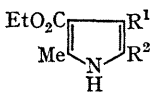
3,5-Diethoxycarbonyl-1,4-dihydro-2,6-dimethylpyridine-4-carboxylic acid (1) readily prepared by a Hantzsch synthesis,[1] gives three products [compounds (3) (ref. 2), (7) (ref. 3), and (8)] when heated above its melting point (240°). This rearrangement also occurs in solution, when the nature of the products is dependent upon the solvent (see Table).



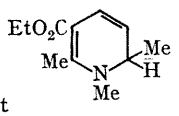
(1) R=H
(2) R=Me



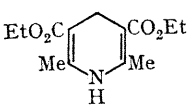
	R^1	R^2	R^3
(3)	CO_2Et	Me	Me
(4)	Me	CO_2Et	Me
(5)	Et	CO_2Et	Me
(6)	Et	Me	CO_2Et



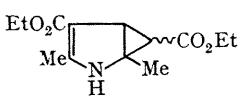
	R^1	R^2
(7)	H	Me
(8)	$CH_2 \cdot CO_2Et$	Me
(9)	Me	$CH_2 \cdot CO_2Et$
(10)	Me	Me
(11)	Me	H



(12)



(13)



(14)

The previously described pyrrole (8)[4] was prepared from (7) by the addition of ethoxycarbonylcarbene (ethyl diazoacetate and copper powder at 120°).[5] The nature of the pyrrole (9) was demonstrated by its conversion into (10),[6] itself obtained from (8) by selective saponification of the ethoxycarbonylmethyl ester group and pyrolysis of the acid thus prepared.[5] Finally, the pyrrole (9) was prepared from (11) by addition of ethoxycarbonylcarbene.[7]

The pyridine (4), shown by the n.m.r. spectrum to be unsymmetrical, was converted into 2,3,5,6-tetramethylpyridine, which could also be prepared from (3) by reduction with lithium aluminium hydride, conversion of the resulting diol into the dichloride by thionyl chloride, and hydrogenolysis of the free base.[8]

The position of the ester group in the pyridine (4) was determined by comparison of its u.v. spectrum with those of (5) and (6).† The close similarity of the absorption spectra of (4) [λ_{max} 227 nm. (ϵ 8200), 283 (4600)] and (5) [λ_{max} 225 nm. (ϵ 11,000), 282 (5500)] and the difference of that of (4) and (6) [λ_{max} (MeOH) 230·5 nm. (ϵ 10,800), 271·5 (5050)] are in agreement with structure (4).

The methyl ester, the sodium salt and the amide of the acid (1) were unchanged under the conditions of the rearrangement. The 1,2- or 1,4-dihydropyridines (12) and (13)[9] on being heated to 240°, or in refluxing butyric acid, produced none of the products obtained from the acid (1), and therefore cannot be intermediates in the rearrangement. The *N*-methyl derivative of the acid (1) produces the corresponding *N*-methyl derivatives of (7), (8), and (9). The acid (2), with a 4-methyl group, undergoes a rearrangement of a similar character which will described elsewhere.

The mechanism for this rearrangement, currently under investigation postulates a central role for the cyclopropanes (14).

We are indebted to the firm of Nobel–Bozel for a generous gift of glyoxylic acid.

Yield of the rearrangement products of the acid (1).

Solvent (temp.; time)	Product (mol. %)				
	(3)	(7)	(8)	(9)	(4)
Without solvent (250°; 5 min.)	7	43	50	—	—
Diglyme (160°; 24 hr.)	5	Traces	35	24	0·5
Butyric Acid (162°; 11 hr.)	13·5	35	17	11·5	5
4-Ethylpyridine (164°; 6 hr.)*	3	7	56		

* Starting material (21%) recovered.

(*Received, November 7th*, 1968; *Com.* 1520.)

† Prepared from the corresponding known methyl ketones *via* the thioacetal (E. M. Bottonff, R. G. Jones, E. C. Karnfeld, and M. J. Mann, *J. Amer. Chem. Soc.*, 1951, **73**, 4380).

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