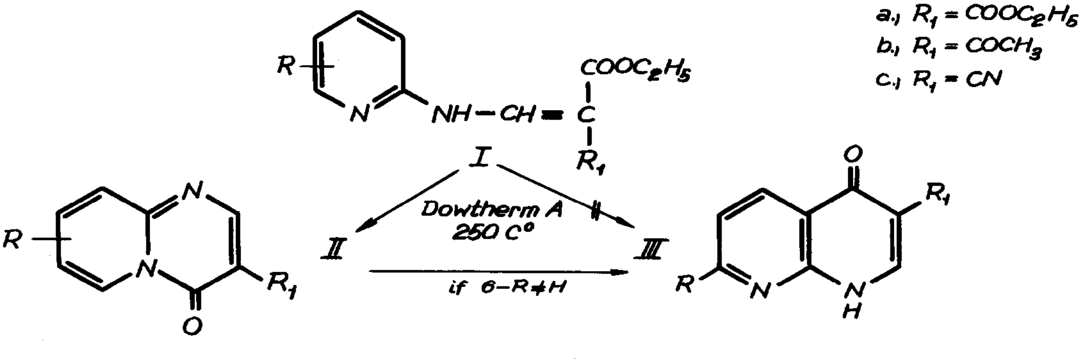
Tetrahedron Letters No. 12, pp 1019 - 1020, 1975. Pergamon Press. Printed in Great Britain.

NITROGEN BRIDGEHEAD COMPOUNDS III.* NEW RING TRANSFORMATION I.

Zoltán Mészáros and István Hermecz
CHINOIN Pharmaceutical and Chemical Works, Budapest

(Received in UK 9 October 1974; accepted for publication 12 February 1975)

Lappin[1] was first to observe that when Ia were heated in Dowtherm A at 250 C°, 2 types of products were formed, depending on the position of the substituent in the pyridine ring: IIa were obtained if the pyridine ring was not substituted in position 6; while 6-substituted pyridines /R=6-Me, 6-OEt/ gave IIIa. Lappin presumed that in the latter case because of the steric hindrance of the 6-R ring-closure on the ring N was prevented and so it took place directly on the carbon atom in position 3. Later, however Antaki[2] found that cyclization of Ib,c by vacuum distillation even in case R=6-Me, led to the corresponding IIb,c instead of IIIb,c /R=7-Me/. We reported[3] that cyclising Ia /R=6-alkyl/ in $POCl_3$-PPA at 130-40 C° we obtained IIa /R=6-alkyl/. Under the same conditions Ib /R=6-Me/ decomposed and Ic /R=6-Me/ failed to react. When the course of the cyclization of Ia /R=6-Me/ performed in Dowtherm A was followed by TLC /Kieselgel G, PhH-MeOH=4:1/, between the spots of Ia /R=6-Me, Rf=0,81/ and the formed IIIa /R=7-Me, Rf=0,39/ a third spot Rf=0,53 identified unambiguously as IIa /R=6-Me/ was detected on the cromatogram. On slow heating of the reaction mixture the



spot of IIa /R=6-Me/ appeared first /at 160-180 C^{o}/, and that of IIIa /R=7-Me/ became visible at a higher temperature only /180-200 C^{o}/.

Performing cyclization of Ib,c /R=6-Me/ in paraffin oil at 300 C^{o}, in contrast to Antaki, we failed to obtain the corresponding IIb,c /R=6-Me/, but obtained IIIb [R=7-Me; mp: > 300 C^{o} /DMF/; Y :80%; UV /EtOH/ 321nm /lgε 4,07/; 261 /4,24/; 255i /4,20/] and IIIc [R=7-Me; mp: > 300 C^{o} /DMF/; Y:60%; UV /EtOH/: 327 /4,02/ ; 318i /3,98/; 254,5 /4,24/; 247 /4,19/] /In the reaction of Ib /R=6-Me/ performed in Dowtherm A after 2 hours IIIb /R=7-Me/ was obtained in 65 % yield, while Ic /R=6-Me/ failed to react./

The above facts lead to the conclusion that cyclization of I in the first step always occurs on the ring N, i.e. II are formed which under the given conditions may andergo thermic isomerization and tranform to III by 1-3 N→C acyl migration Acyl migration is rendered possible by the fact that the 6-R and the 4-oxo-group of II /6-R $\neq$ H/ are practically in the same plane and as a consequence of it C_4-N_5 bond subjected to strong strain, splits up readily upon the attact of suitable energy. /According to the X-ray investigations[4] the C_4-N_5 bond length in IIa /R=6-Me/ is 1,472Å./

Corresponding to the above theoretical consideration, IIa /R=6-Me/ prepared in $POCl_3$-PPA reaction[3] could be transformed to IIIa /R=7-Me, Y:80%/ by heating in Dowtherm A. II /R=H/ could not be isomerized thermically.

The presence of sterically large substituents /e.g. Br/ in position 6 of Ia appears to prevent ring closure. Thus, our earlier endeavours[3] to cyclisize Ia /R=6-Br/ in $POCl_3$/PPA failed. Ia /R=6-Br/ was regained unchanged from the reaction mixture. Upon heating in Dowtherm A the compound decomposed[1].

REFERENCES AND NOTES:

* to be considered Part II: J.Chem.Soc.Perkin I 1974 1753;
Part I: see ref. 3./ of this article;

1./ G.R. Lappin: J.Am.Chem.Soc. 70 3348 /1948/;

2./ H. Antaki: J.Am.Chem.Soc. 80 3066 /1958/;

3./ Z. Mészáros, J. Knoll, P. Szentmiklósi, Á. Dávid, G. Horváth, I. Hermecz: Arzneim-Forsch. /Drug Res./ 22 815 /1972/;

4./ K. Sasvári, J. Csonka-Horvai, K. Simon: Acta Cryst. B28 2405 /1972/