Tetrahedron Letters No.1, pp. 33-36, 1968. Pergamon Press Ltd. Printed in Great Britain.

FORMATION OF PYRIMIDO[1,2-b]PYRIDAZINES, A NEW BICYCLIC TRIAZAHETEROCYCLIC SYSTEM

B. Stanovnik and M. Tišler

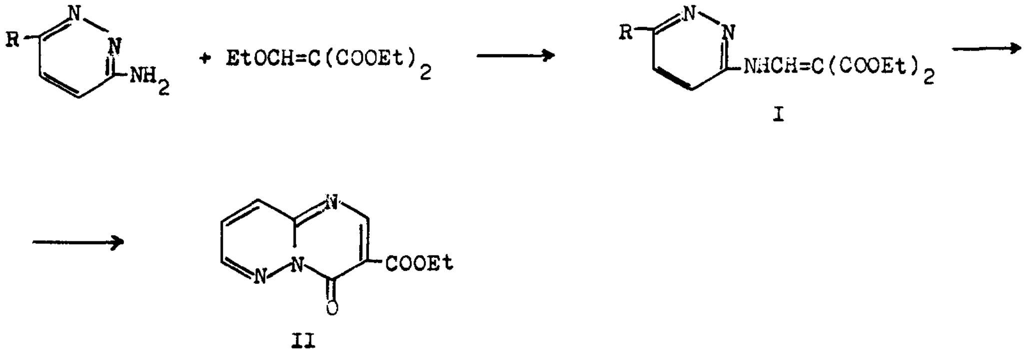
Department of Chemistry, University of Ljubljana,

Ljubljana, Yugoslavia

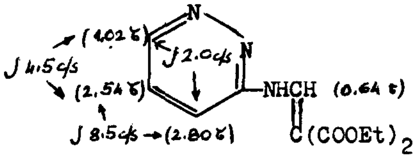
(Received in UK 31 August 1967)

Of the isomeric pyrimido-pyridazines, so far only representatives of two systems are known, the pyrimido[4,5-c]pyridazines (1,2,3) and pyrimido[4,5-d] pyridazines (4). We wish to report now the synthesis of a derivative of the third isomeric system, i.e. pyrimido[1,2-b]pyridazine.

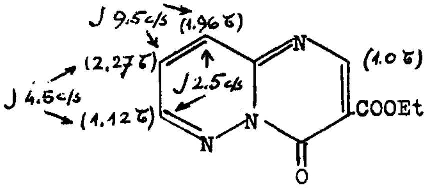
3-Aminopyridazine when condensed with ethyl ethoxymethylenemalonate at 110° afforded ethyl 3-pyridazinylaminomethylenemalonate (I, R = H) in 45% yield, m.p. 130°. UV: λ_{max}^{EtOH} 3160 Å, ϵ = 22,100; IR (Nujol): 3220 (NH), 1681, 1653 cm^{-1}. This, when heated under reflux in diphenyl ether afforded after precipitation with n-hexane the cyclic product (II) in 73% yield, m.p. 169-170°. UV: λ_{max}^{EtOH} 3420 Å, ϵ = 9,360; IR (Nujol): 1724 and 1739 cm^{-1} (CO).



There are known several examples when heterocyclic amines have been condensed with ethyl ethoxymethylenemalonate to form bicyclic systems (5,6,7) and the structural assignment of these has been made principally on the basis of UV spectra. The available spectroscopic data which are discussed, present evidence that also in our case the reaction took place as indicated. Besides the above data, the NMR spectrum of I (R = H) was recorded as a 20% solution in $CDCl_3$ (TMS as internal standard) and the following proton chemical shifts and spin-spin coupling constants were determined:



The NMR spectrum of II (in $CDCl_3$) clearly eliminates the possibility of cyclization on the position 4 of the pyridazine ring and the recorded data are consistent with the pyrimido[1,2-b]pyridazin-4-one skeleton:



Evidently, the order of chemical shifts in the pyridazine ring of II is $H_7 < H_9 < H_8$, coupling constants follow likewise this order and such a correlation was observed earlier with pyridazine (8), pyridazine-N-oxides (9) or imidazo[1,2-b]pyridazines (10). The alternative possible structure, i.e. pyrimido[1,2-b]pyridazin-2-one, can be rejected on the basis of the evidence for the intermediate I and on account of the UV spectrum of II since the isomeric 2-one would be expected to absorb at a shorter wavelength in analogy with the related pyrido[1,2-a]pyrimidones (5,6).

The obtained 3-carbethoxypyrimido[1,2-b]pyridazin-4-one and the starting uncyclized product (I, R = H) are stable in ethanolic solution, but in aqueous, alkaline or acid solution structural changes occur and these can be readily followed spectrophotometrically. II, upon standing in aqueous or 0.1 N NaOH solution for 1 week, is transformed into an open chain compound, identical with that obtained from I (R = H) upon standing in 0.1 N NaOH solution. The spectrum of II in 0.1 N HCl is practically identical with that of I (R = H) after standing in 0.1 N HCl indicating that in the latter case most probably cyclization occured. These changes are consistent with the behaviour of other cyclic lactams.

In the same manner as above, from 3-amino-6-chloropyridazine the corresponding pyridazinylaminomethylenemalonate (I, R = Cl, m.p. 169°, yield 75%) has been prepared, but efforts to cyclize it have so far been unsuccessful.

Satisfactory analytical data have been obtained on every compound described and full details will be published later.

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