Tetrahedron Letters No.44, pp. 4385-4388, 1967. Pergamon Press Ltd. Printed in Great Britain.

RING TRANSFORMATIONS IN REACTIONS OF HETEROCYCLIC COMPOUNDS WITH NUCLEOPHILES

Conversion of pyrimidines into pyrazoles and 1,2,4-triazoles (1)

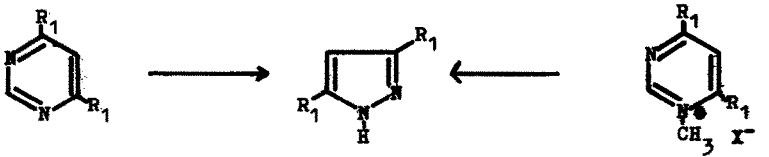
H.C.van der Plas and H.Jongejan
Laboratory of Organic Chemistry of the Agricultural University,
Wageningen, the Netherlands

(Received in UK 26 May 1967)

During the last years reactions of substituted pyrimidines with nucleophiles causing ring transformations, have been reported. Examples of these reactions are the conversions of 2-substituted 4-chloropyrimidines into 2-substituted 4-methyl-s-triazines by potassium amide in liquid ammonia (2,3), the transformation of 5-amino- and 5-methyl-4-chloro-2-phenylpyrimidine into 4-cyano-, resp. 4-ethynyl-2-phenyliminazole by the same reagent (4), the formation of 1-methyl- and 1,4-dimethylpyrazolones-5 when reacting uracil and thymine with methylhydrazine (5), and the conversion of pyrimidine into pyrazole by treatment with sodium hydrazide at low temperature (6).

The recently reported finding that 4-methoxy-5-nitropyrimidine by treatment with hydrazine above 20° is converted into 3-amino-4-nitropyrazole (7) prompts us to report the results of an investigation of the behaviour of pyrimidine and some of its derivatives towards hydrazine at more elevated temperatures.

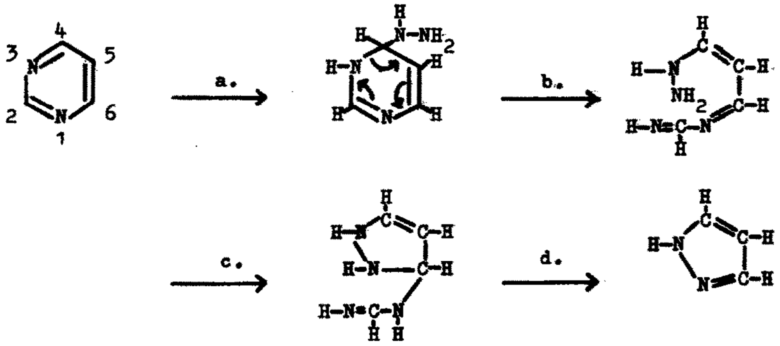
When pyrimidine (I) is reacted with hydrazine hydrate and water in a sealed tube at 130° for 5 hrs, pyrazole (III) is formed in a good yield (75-80%). Under identical reaction conditions 4,6-dimethylpyrimidine (II) is completely unchanged. More drastic conditions (190°, 5 hrs) are required in order to achieve conversion of II into 3,5-dimethylpyrazole (IV, yield: 60-65%). By contrast, the presence of a methyl group attached to the nitrogen atom was found to increase the reactivity of the pyrimidine nucleus towards hydrazine considerably. Both 1-methylpyrimidinium methylsulphate (V) and 1,4,6-trimethylpyrimidinium iodide (VI) are already converted at 45° into pyrazole (III) and 3,5-dimethylpyrazole (IV) resp.



I: $R_1 = H$ III: $R_1 = H$ V: $R_1 = H$; $X^- = {}^-OSO_3CH_3$

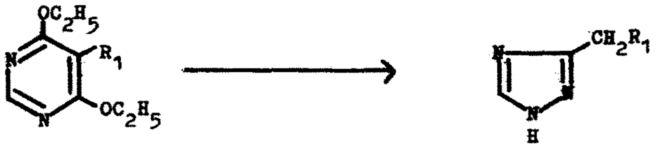
II: $R_1 = CH_3$ IV: $R_1 = CH_3$ VI: $R_1 = CH_3$; $X^- = I^-$

The mechanism of the hydrazinolysis of pyrimidine can be considered to invelve the following steps: a. addition of hydrazine to the N_3- C_4(N_1- C_6)bond, b.ring opening by breakage of the N_3- C_4(N_1- C_6)bond, c. ring closure, d. aromatisation by loss of the N_1+ C_2+ N_3 skeleton originally present in the pyrimidine nucleus.



According to the same mechanism 4,6-dimethylpyrimidine and the N-methyl pyrimidinium salts can be transformed into the corresponding pyrazoles.

When 4,6-diethoxypyrimidine (VII) was reacted with hydrazine and water at 210° for 5 hrs surprisingly no pyrazole derivative was obtained but a product, m.p.96°, to which, based on quantitative elemental analysis, IR- and NMR-data (8), the structure of 3-methyl 1,2,4-triazole (VIII) could be assigned (yield: 55-60%; $C_3H_5N_3$ requires C 43.69; H 6.07. Found: C 43.67; H 6.23%). This conclusion was affirmed by mixed melting point determination with an authentic specimen (m.p. 96°, lit.(9): 94°).

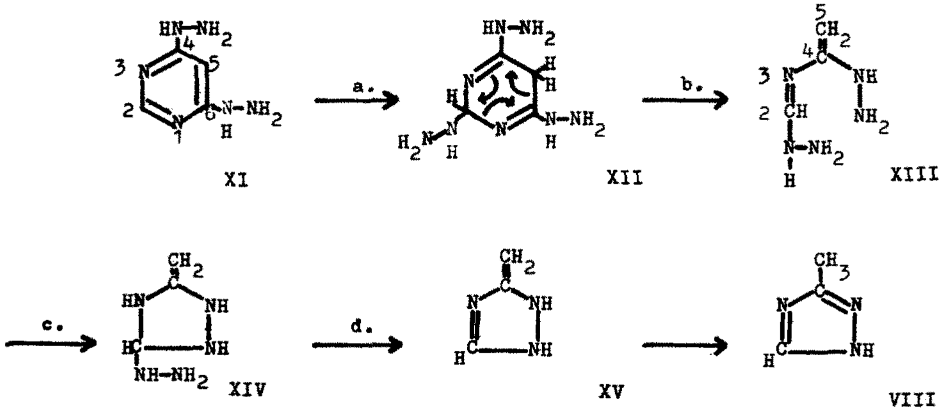


VII: R_1= H VIII: R_1= H

IX: R_1= CH_3 X: R_1= CH_3

In order to establish from which carbon atom of the pyrimidine ring the carbon atom of the methyl group is originated, the behaviour of 4,6-diethoxy-5-methylpyrimidine (IX) towards hydrazine was investigated. When IX was reacted at 210° for 15 hrs a hygroscopic compound was found to be formed, which was identical with an authentic specimen of 3-ethyl-1,2,4-triazole (X)(10). Yield 30-35%. This result clearly indicates that both the 5-methyl group and the 5-carbon atom of the pyrimidine ring contribute to the formation of the ethyl group in X. Moreover, it firmly establishes that in the pyrimidine-1,2,4-triazole transformation, breakage of a C_4-C_5(C_5-C_6) bond has to take place.

Besides VII, also 4,6-dihydrazinopyrimidine (XI) was found to be converted into VIII, when treated with an aqueous solution of hydrazine at 210° for 5 hrs. It might be possible that in the conversion of VII into VIII first the ethoxy groups are replaced by hydrazino groups and that subsequently XI is transformed into VIII. Tentatively the following multi-stage mechanism of the ring transformation XI ⟶ VIII is advanced:



a. addition of hydrazine to the 2,5-position of the pyrimidine ring, yielding the 2,5-dihydro compound XII, b. opening of the ring of XII by fission of the C_5- C_6 bond and the N_1- C_2 bond affording XIII, c. ring closure to XIV, d. conversion of XIV into XV by splitting of hydrazine.

Further work is in progress fo investigate the general scope of these transformations.

We are indebted to Drs.P.Smit for recording and interpreting the IR- and NMR-spectra.

REFERENCES

1. IXth communication from this Laboratory on Reactivity of pyrimidine derivatives. VIIIth paper: H.W.van Meeteren and H.C.van der Plas, Rec.Trav.Chim. 86, 567 (1967).
2. a. H.C.van der Plas, Miss B.Haase, B.Zuurdeeg and Miss M.C.Vollering, Rec. Trav.Chim. 85, 1101 (1966). b. H.W.van Meeteren and H.C.van der Plas, Rec.Trav. Chim. 86, 15 (1967).
3. H.W.van Meeteren, Thesis, Leiden 1967.
4. H.W.van Meeteren and H.C.van der Plas, Tetrahedron Letters, No.37, p.4517 (1966).
5. F.Lingen and H.Schneider-Bernlöhr, Liebigs Ann.Chem. 686, 135 (1965).
6. Th.Kauffmann, Angew.Chemie 76, 215 (1964).
7. M.E.C.Biffin, D.J.Brown and Q.N.Porter, Tetrahedron Letters No.21, p. 2029 (1967).
8. See for a recent report on the NMR-data of 3-substituted 1,2,4-triazoles W.Freiberg, C.F.Kröger and R.Radeglia, Tetrahedron Letters No. 22, p.2109 (1967).
9. R.G.Jones and C.Ainsworth, J.Am.Chem.Soc. 77, 1539 (1955).
10. G.B.Bryant Bachman and L.V.Heisey, J.Am.Chem.Soc. 71, 1985 (1949).