

HETARYNES VIII¹

AMINATIONS OF 6-SUBSTITUTED 5-BROMOPYRIMIDINES
WITH POTASSIUM AMIDE IN LIQUID AMMONIA, POSSIBLY INVOLVING
A 5,6 (=4,5)-PYRIMIDYNE AS INTERMEDIATE

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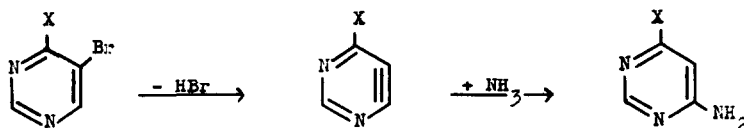
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IN recent years much interest is centered around studies on rearrangements occurring during reactions of halogenated aromatic heterocycles with potassium amide in liquid ammonia or lithium piperidide in an ethereal solution of piperidine. The formation of rearranged amino products indicates a reaction in which an elimination-addition mechanism occurs, a hetaryne being the intermediate. Based on the results of these studies the following hetarynes are advanced: 3,4-pyridyne^{2,3,4}, 2-, 5- and 6-ethoxy-3,4-pyridyne^{2,3,5}, 4-ethoxy-2,3-pyridyne^{1,2,3,5,6}, 4,6-diethoxy-2,3-pyridyne⁶, 5-bromo-4-ethoxy-2,3-pyridyne⁶, 2,3-pyridyne-N-oxide¹, 4-ethoxy-2,3-pyridyne-N-oxide¹, 3,4-quinolyne⁷,

1. Previous paper on hetarynes from this laboratory: R.J.Martens and H.J.den Hertog, Rec.Trav.Chim.83 (1964) in the press.
2. M.J.Pieterse and H.J.den Hertog, Rec.Trav.Chim.80, 1376 (1961).
3. M.J.Pieterse, Thesis Amsterdam 1962.
4. Th.Kauffmann and F.F.Boettcher, Angew.Chem.73, 65 (1961).
5. H.J.den Hertog, M.J.Pieterse and D.J.Buurman, Rec.Trav.Chim.82 1173 (1963).
6. M.J.Pieterse and H.J.den Hertog, Rec.Trav.Chim.81, 855 (1962).
7. Th.Kauffmann, F.F.Boettcher and J.Hansen, Liebigs Ann.Chem.659 102 (1962).

1,5-naphthyridyne-3,4⁸, 1-methyl-2-phenyl-4,5-pyridazyne-dion (3,6)⁹ and 3,4-isoquinolyne¹⁰.

Some months ago, in a short communication Schwan and Tieckelmann¹¹ presented evidence for the occurrence of 2-methyl-4,5-pyrimidyne. This evidence was provided by the formation of a mixture of 2-methyl-4-amino and some 2-methyl-5-aminopyrimidine (total yield < 5%) when 2-methyl-5-chloropyrimidine was treated with sodium amide in liquid ammonia. The appearance of that paper prompts us to publish some preliminary results obtained in this laboratory thus far on the reaction of 5-bromo-4-phenylpyrimidine (I), 5-bromo-4-methoxypyrimidine (II) and 5-bromo-4-hydroxypyrimidine (III) with potassium amide in liquid ammonia.



I : X = C₆H₅
 II : X = OCH₃
 III: X = OH

IV : X = C₆H₅; yield: 15%
 V : X = OCH₃; yield: 70%
 VI : X = OH ; yield: 75%

8. W.Czuba, Rec.Trav.Chim.82,997 (1963).

9. Th.Kauffmann and A.Risberg, Tetrahedron Letters No.22, 1459 (1963).

10.Th.Kauffmann and J.Hansen, see reference 9, note 3.

11.Th.J.Schwan and H.Tieckelmann, J.Org.Chem.29, 941 (1964).

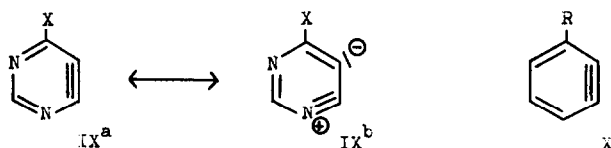
On treatment of 5-bromo-4-phenylpyrimidine (I) with potassium amide (molar ratio 1 : 4) in liquid ammonia for 3 hrs at -33° , 6-amino-4-phenylpyrimidine (IV, m.p. : 225-226^o) was isolated as the sole amino product. The structure of IV was established by a mixed melting point determination with a specimen (m.p.: 228-228.5^o), obtained from 6-chloro-4-phenylpyrimidine (VII) by heating with ammonia. An analysis by gas-liquid chromatography of the crude reaction mixture of the amination of I, using a column (k 119) packed with sodium carbonate and Carbowax 20 M on Chromosorb (weight ratio = 8 : 20 : 72) at 250^o and hydrogen as carrier gas, revealed that no 5-amino-4-phenylpyrimidine (VIII) was formed.

From the reaction mixture obtained by treating 5-bromo-4-methoxypyrimidine (II) with potassium amide 6-amino-4-methoxypyrimidine (V, m.p.: 145-146^o) was isolated. In a mixed melting point determination with an authentic specimen, prepared from 6-amino-4-methoxy-2-methylthiopyrimidine¹², no depression was observed. A g.l.c. analysis of the reaction mixture on a column (k 61) filled with sodium carbonate and Polywachs 2000 on Chromosorb (weight ratio = 14 : 20 : 66) at 200^o, using hydrogen as carrier gas, established that if the isomeric 5-amino-4-methoxypyrimidine is present at all, its amount does not surpass 2% of the amount of V.

12. According to W. Pfleiderer and E. Liedek, Liebigs Ann. Chem. 612, 163 (1958).

A complete rearrangement also occurs in the amination of 5-bromo-4-hydroxypyrimidine (III) with potassium amide. 6-Amino-4-hydroxypyrimidine (VI, m.p.: 267-269°) was isolated as the sole reaction product. It was identified by mixed melting point determination with an authentic specimen, prepared from 6-amino-4-hydroxy-2-methylthiopyrimidine¹³.

The formation of 4-substituted 6-aminopyrimidines from the corresponding 4-substituted 5-bromopyrimidines is consistent with a hetaryne-type mechanism, involving IX^{a-b} as intermediate. Because of resonance and inductive effects of both nitrogen atoms, the hydrogen in the 6-position is highly acidic to form easily the dehydro compound IX, which, corresponding to all 3-azabenzynes, is stabilized by resonance (IX^{a-b}).



From the results obtained thus far it can be concluded that addition of ammonia to a 5,6 (= 4,5)-pyrimidyne is very specific, as in preference or exclusively a 6-amino product is obtained irrespective of which substituent is present in the 4-position. This is in agreement with the work of Schwan

13. According to B.R.Baker, J.P.Joseph and R.E.Schaub, J.Org.Chem. 19, 632 (1954).

and Tieckelman¹¹. This orienting effect is remarkable as in this laboratory a great discrepancy is found in the directive influence of the methoxy group and the ionised hydroxy group on the addition of ammonia to 3-substituted benzyne (X). Whereas from 3-methoxy-benzyne (X, R = OCH₃) almost exclusively the m- amino compound is formed¹⁴, it appeared that from X(R = O⁻) mainly the o-amino compound is obtained¹⁵. The formation of only 6-amino compounds from 4-substituted 5,6-pyrimidynes may indicate that the contribution of the resonance structure IX^b is really so important that, because of deactivation of the 5-position, a nucleophilic attack of the amide ion takes place only on position 6. A similar orienting effect is observed in the addition of ammonia to 4-substituted 2,3-pyridynes, forming almost exclusively 2-amino compounds¹⁶.

The synthesis of the compounds I, II, VII and VIII were performed as follows:

5-Bromo-4-phenylpyrimidine(I). 4-Phenyl-2-thiouracil¹⁷ was desulfurized with Raney nickel and the 6-hydroxy-4-phenylpyrimidine obtained was converted with bromine in glacial acetic acid into 5-bromo-6-hydroxy-4-phenylpyrimidine(m.p.:246-247°).

14. Cf. J.D. Roberts, C.W. Vaughan, L.A. Carlsmith and D. Semenov, J. Am. Chem. Soc. **78**, 611 (1956).

15. G.E.R. de Graaff, W.Ch. Melger and H.J. den Hertog, Rec. Trav. Chim.: in the press.

16. R.J. Martens and H.J. den Hertog, Rec. Trav. Chim.: in the press.

17. T.B. Johnson and E.A. Hemingway, J. Am. Chem. Soc. **37**, 378 (1915).

This compound was heated with phosphorochloride to yield 5-bromo-6-chloro-4-phenylpyrimidine (m.p.: 83-84°) from which 5-bromo-6-hydrazino-4-phenylpyrimidine (m.p. : 182-183°) was obtained by refluxing with an ethanolic solution of hydrazine hydrate. Oxidation of this hydrazinopyrimidine with a suspension of silver acetate in water gave I (m.p. : 89-90°) in an overall yield of about 40%.

5-Bromo-4-methoxypyrimidine (II). This compound was synthesized from 5-bromo-4-chloropyrimidine¹⁸ by refluxing with a methanolic solution of sodium methylate. Yield: 76%; m.p.: 66-67.5°.

6-Chloro-4-phenylpyrimidine (VII). By reacting 6-hydroxy-4-phenylpyrimidine with phosphorus pentachloride at 140° for some hours VII was obtained in a yield of 90%; m.p. : 96-97.5°.

5-Amino-4-phenylpyrimidine (VIII). Ammonolysis of I with conc. ammonia and cupric sulphate at 135° in a sealed tube for 50 hrs gave VIII in a yield of 51%; m.p.: 113-115°.

All compounds used in this study (I-VIII) were checked by elementary analyses.

18. J. Chesterfield, J.F.W. McOmie and E.R. Sayer, J. Chem. Soc. 1955, 3478.

Acknowledgement

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