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HETARYNES XI[1]

Aminations of 4-substituted 5-bromopyrimidines with potassium amide in liquid ammonia, possibly involving a 5,6(= 4,5)-pyrimidyne as intermediate[2].

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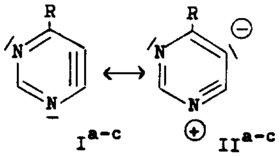
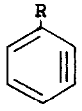
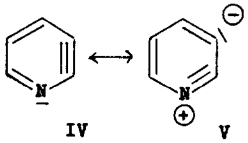
The mechanism of the amination of 4-substituted 5-bromopyrimidines with potassium amide in liquid ammonia has been discussed in terms of an elimination-addition process, involving 4-substituted 5,6-pyrimidynes as intermediates[3]. In all 4-substituted pyrimidynes investigated (I^{a-c}) the addition of the nucleophilic amide ion to the "triple bond" occurs exclusively on the 6-position, only 4-substituted 6-aminopyrimidines being formed.



I^{a-c} II^{a-c}



III



IV V

a: $R=C_6H_5$; b: $R=OCH_3$; c: $R=O^-$

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[1] Hetarynes X, R.J.Martens,H.J.den Hertog and M.van Ammers, Tetrahedron Letters No.43, 3207 (1964).

[2] 4th Communication from this laboratory on pyrimidines.

[3] H.C.van der Plas and G.Geurtsen, Tetrahedron Letters,No.31, 2093 (1964).

This exclusive orientation was the most surprising for the pyrimidyne I[c] as the directive influence of this anionic group in the benzyne III ($R=O^-$) has been determined to be nearly exclusive ortho[4]. Therefore, it was concluded that in these pyrimidynes the resonance interaction between the sp^2-carbon orbitals and the sp^2-nitrogen orbital, containing the lone pair, was really important (I ↔ II), as it leads to a deactivation of position 5 and therefore can account for the non-formation of a 5-aminopyrimidine derivative. Recent MO calculations on resonance interactions in 2,3-pyridyne (IV ↔ V), a hetaryne with the same structural feature as I ↔ II, clearly show that in IV ↔ V also an exclusive substitution in the 2-position will occur[5].

In order to obtain more information on the mode of addition of ammonia to 4-substituted 5,6-pyrimidynes, the reactivity of 5-bromo-4-*t*-butylpyrimidine, 4-amino-5-bromopyrimidine and 5-bromo-4-methylpyrimidine towards potassium amide in liquid ammonia(-33°) was studied. In the reaction products obtained the ratio of the amino products was determined by gas chromatographic analysis (GLC) or infrared spectroscopy (IR). The results of these experiments are summarized in the table.

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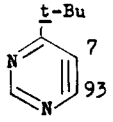
[4] G.B.R.de Graaff, W.Ch.Melger and H.J.den Hertog, *Rec.Trav.Chim.* in press.

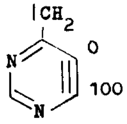
[5] H.L.Jones and D.L.Beveridge, *Tetrahedron Letters* No.**24**, 1577(1964).

4-substituted 5-bromopyrimidine	Time of reaction (hrs)	Yield of amino product (%)	Ratio of the isomeric 5- and 6-aminopyrimidine derivatives	
			5-isomer	6-isomer
4-*t*-butyl-5-bromopyrimidine	5	14	7	93(GLC)
4-methyl-5-bromopyrimidine	11	16	0	100(GLC)
4-amino-5-bromopyrimidine	3	95	0	100(IR)
4-hydroxy-5-bromopyrimidine	3	75	0	100(IR)

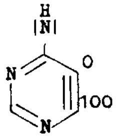
The rearrangements in these reactions observed, are consistent with a hetaryne-type mechanism, involving the dehydro compounds VI, VII and VIII. Because of the presence of a strong base (NH_2^-) it is very likely that in the hetarynes VII and VIII not the methyl- or amino group as such, but its conjugate base is the substituent really present in the 4-position.



VI



VII



VIII

Of these three groups it is only the $\bar{N}H$-group, which directive influence is known to be exclusively <u>ortho</u>[4]. However, applying the orientation rules as given by Roberts c.s.[6], both the *t*-butyl group and the $\bar{C}H_2$-group can be expected to be <u>ortho</u>/<u>meta</u> directing because of the + I-effect of these groups.

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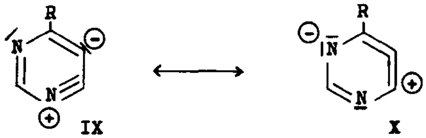
6. J.D.Roberts,C.W.Vaughan, L.A.Carlsmith and D.Semenow, <u>J.Amer.Chem.Soc.</u>**78**,611(1956).

From the ratio of addition of ammonia to the arynes VII and VIII it can be concluded that the ortho-directing influence of both -$\overline{N}H$ and $\overline{C}H_2$ groups is completely offset by the directive influence of the nitrogen in position-1, favouring 6-substitution. A similar orienting effect is observed in the addition of ammonia to a series of 4-substituted 2,3-pyridynes, forming almost exclusively 2-amino compounds[7].

The small amount of 5-amino-4-t-butylpyrimidine formed in the reaction of 5-bromo-4-t-butylpyrimidine with potassium amide clearly indicates that the pattern of addition of ammonia to this pyrimidyne is not governed exclusively by the orienting influence of the nitrogen in position-1 but is also dependent on the substituent present in position 4.

From all results obtained thus far, resonance contributions leading to a deactivation of position 5, seem likely (see IX, R=CH_3, C_6H_5, $C(CH_3)_3$, $|\overline{O}$, $\overline{N}H$, $\overline{C}H_2$). If the almost exclusive addition to the 6-position can also be ascribed to important contributions of structures with accumulated C-C bonds as pictured in X does not seem impossible.



IX X

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[7] R.J.Martens and H.J.den Hertog, Rec.Trav.Chim. in press.

Very recently mesomerism of this type has been advanced in the hetarynes 3,4-dehydrocarbostyril, 3,4-dehydrocoumarin and 1-methyl-2-phenyl-4,5-dehydropyridazin-dion(3,6)[8].

The syntheses of the pyrimidine compounds, mentioned in these studies, have been described in a forthcoming paper[9].

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8. Th.Kauffmann, A.Risberg, J.Schulz and R.Weber, Tetrahedron Letters No 47, 3563 (1964).

9. H.C.van der Plas, Rec.Trav.Chim. in press.