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SELECTIVE ACID HYDROLYSIS OF 2-SUBSTITUTED-5-DIMETHYLAMINOMETHYLENEAMINOPYRIMIDINES TO 5-AMINO- AND 5-HYDROXYPYRIMIDINES

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Conditions are described for the selective acid hydrolysis of 2-substituted-5-dimethylaminomethyleneamino-pyrimidines in 0.2-2 M sulfuric acid, to give high yields of the corresponding 5-amino- and difficultly accessible 5-hydroxypyrimidines.

According to a literature report [1], acid hydrolysis of 2-substituted-5-dimethylaminomethyleneaminopyrimidines affords 5-formylamino- or 5-amino-compounds on treatment with 0.2 M acetic acid or 0.02 (0.2) M sulfuric acid, respectively. It has, however, been shown that treatment of 2,4(6)-OH, CH_3,NH_2-substituted 5-aminopyrimidines with 20% sulfuric acid gives the corresponding 5-hydroxypyrimidines [2, p. 236], which forms one method for the preparation of these difficultly accessible pyrimidine derivatives. Information on methods of preparation of 2-aryl-5-amino- or 2-aryl-5-hydroxypyrimidines which do not contain additional substituents in the 4- and 6-positions of the pyrimidine ring are of a fragmentary nature, and are not sufficiently general. For example, the reduction of 2-aryl-5-nitropyrimidines has been reported [3], and the synthesis of 2-phenyl-5-hydroxypyrimidine from 2-phenyl-4-hydroxy-5-methoxypyrimidine [4].

It was therefore desirable to examine the acid hydrolysis of 2-aryl-5-dimethylaminomethyleneaminopyrimidines over a wide pH range, in order to develop a convenient method of synthesis of the corresponding 5-amino- and 5-hydroxypyrimidines. The required 2-aryl compounds (IIIa-e) were obtained by us by reacting the propenylidenamine perchlorate (I) with the amines (IIa-e), as in [5].

It was found that acid hydrolysis of (IIIa, c-e), by boiling in 0.2 M sulfuric acid for 30-110 min, gave, as in [1], the 5-amino-compounds (IVa, c-e) in higher yields than were obtained by reduction of the nitro-compounds [3], and when the acidity of the solution was increased to 1 M sulfuric acid for 30-60 min, the 2-aryl-5-hydroxypyrimidines (Va, c-e) were obtained readily in high yields. The use of 2 M sulfuric acid (~20%; cf. [2]) for the hydrolysis of (IIIa-e) also afforded the 5-hydroxypyrimidines, but after only 15-30 min. In the case of (Va-c), increasing the reaction time resulted in a decrease in the yields of hydrolysis products, and made considerably more difficult their isolation and purification as a result of resinification of the reaction mixture (see, for example, the preparation of (Vb), Table 1).

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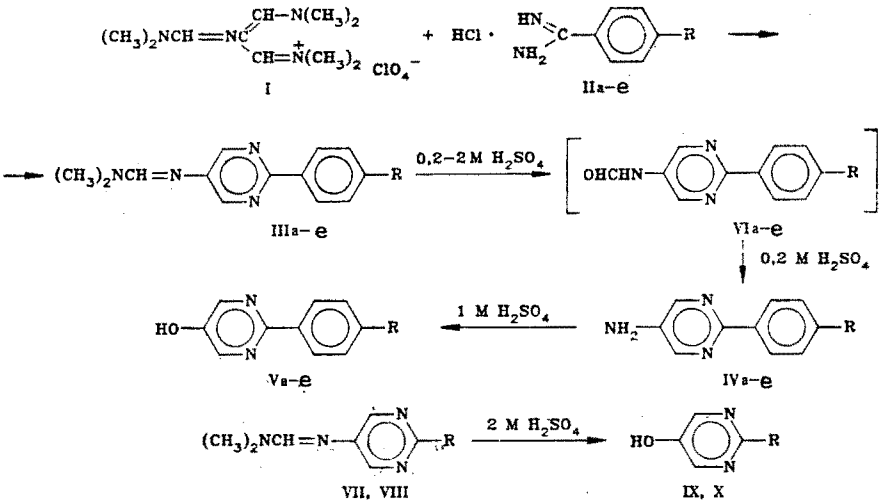
In order to establish the sequence of steps in the acid hydrolysis of (IIIa-e) to the correpsonding 5-hydroxy-compounds, we examined the reactions of (IIId) when the acidity of the medium and the reaction times were varied. The hydrolysis products were examined by mass spectrometry. Using 0.2 M sulfuric acid, after 10 min (IIId) and (VId) were formed, after 15 min (IIId), (IVd), and (VId), and after 110 min (IVd); when 1 M sulfuric acid was used, after 15 min (IIId), (IVd), (Vd), and (VId) were formed, after 30 min (IVd) and (Vd), and after 60 min, (Vd); when 2 M sulfuric acid was used, after 10 min (IIId), (IVd), and (Vd) were formed, after 20 min (IIId) and (Vd), and after 30 min (Vd).

These observations show that the acid hydrolysis of (IIIa-e) proceeds via the intermediate formation of the 5-formylamino-compounds, as shown by the presence in the hydrolysis products of the pyrimidine (IIId) of a compound of molecular mass 244, corresponding to 2-(p-nitrophenyl)-5-formylaminopyrimidine (VId) (cf. [1]), together with the subsequent formation, as the acidity is increased, of the 5-amino- and 5-hydroxy-compounds (IVd) and (Vd). The proposed route for the formation of 5-hydroxypyrimidines is confirmed by hydrolysis of the 5-aminopyrimidines (IVa) and (IVe), since when these are boiled in 1 M sulfuric acid for 60 min, 90% yields of the hydroxy-compounds (Va, e) are obtained, and the 5-formylaminopyrimidine (VIf) readily affords the 5-hydroxy-compound (Vf) on boiling in 2 M sulfuric acid for 20 min.



II—VI a R=$(CH_2)_5CH_3$, b R=$(CH_2)_6CH_3$, c R=$O(CH_2)_5CH_3$, d R=NO_2, e R=Br; VII, IX R=Cl; VIII, X R=SCH_3

Finally, in order to extend the scope of this method of preparation of the difficultly accessible 5-hydroxypyrimidines, the reactions of 2-chloro- (VII) and 2-methylthio-5-dimethylaminomethyleneaminopyrimidine (VIII) were examined. According to [1], on boiling (VII) and (VIII) in 0.2 M sulfuric acid, the 5-amino-compounds are obtained. We have found that increasing the acidity of the medium to 2 M sulfuric acid results in the formation of 2-chloro- (IX) and 2-methylthio-5-hydroxypyrimidine (X) in high yields, which is a considerable improvement on the previously described multistage synthesis of these compounds [6].

EXPERIMENTAL

Molecular masses were measured by mass spectrometry on a high-resolution Finnigan MAT 8200 apparatus.

The required 2-aryl-5-dimethylaminomethyleneaminopyrimidines (IIa-d) were obtained as in [5], and recrystallized: (IIIa) from aqueous alcohol (1:1), (IIIb) from alcohol–petroleum ether (1:10), (IIIc) from alcohol, and (IIId) from toluene. Compounds (IIIe) was obtained as described in [3]. The elemental analyses of the products for C, H, and N were in agreement with the calculated values.

2-(p-Nitrophenyl)-5-aminopyrimidine (IVd). A mixture of 10 ml of 0.2 M sulfuric acid and 0.5 g (1.8 mmoles) of the pyrimidine (IIId) was refluxed for 90 min, cooled to 20°C, the solid filtered off, washed on the filter with water until neutral, and dried to give 0.38 g of the amine (IVd).

Obtained similarly were (IVa), (IVc) [reaction time 30 min, yield 90%, mp 130-131°C (lit. mp 129-131°C [3])] and (IVe) [yield 99%, mp 250-251°C (lit. mp 249-250°C [3])].

TABLE 1. Preparation Conditions and Properties of (III-V)

Compound	Empirical formula	mp, °C	Conc. H_2SO_4, mole/liter	Reaction time, min	M^+ (m/z) found	M^+ (m/z) calc.	Yield, %
IIIa	$C_{19}H_{25}N_4$	66	—	—	—	—	99
IIIb	$C_{20}H_{28}N_4$	71...72	—	—	—	—	54
IIIc	$C_{19}H_{26}N_4O$	109...110	—	—	—	—	72
IIId	$C_{13}H_{13}N_5O_2$	222...223	—	—	—	—	92
IVa	$C_{16}H_{21}N_3$	98	0,2	110	—	—	98
IVd	$C_{16}H_{21}N_3$	320...321	0,2	90	216,0641	216,0647	97
Va	$C_{16}H_{20}N_2O$	126...128	1	60	256,1575	256,1576	89
			2	15			91
Vb	$C_{17}H_{22}N_2O$	142...144	2	240	—	—	15
Vc	$C_{16}H_{20}N_2O_2$	116...118	1	30	272,1526	272.1525	95
			2	15			97
Vd	$C_{10}H_7N_3O_3$	254	1	60	217,0478	217,0488	99
			2	30			99
Ve	$C_{10}H_7BrN_2O$	208....209	2	60	249,9756	249,9742	99

2-(p-Nitrophenyl)-5-hydroxypyrimidine (Vd). A mixture of 10 ml of 1 (or 2) M sulfuric acid and 0.5 g (1.8 mmoles) of (IIId) was boiled under reflux for 60 (or 30) min, cooled to 20°C, and (Vd) isolated as for (IVd).

Obtained similarly were the hydroxy-compounds (Va-c, e) in 83% yield from (IIIa-c, e), and in 90% yield from the aminopyrimidines (IVa, e).

2-Phenyl-5-hydroxypyrimidine (Vf). A mixture of 5 ml of 2 M sulfuric acid and 0.35 g (1.8 mmoles) of the 5-formylaminopyrimidine (VIf) [3] was boiled under reflux for 20 min, cooled to 20°C, and filtered. The filtrate was extracted with chloroform (3 × 30 ml), the chloroform extracts combined, washed with water until neutral, dried over $MgSO_4$, the chloroform removed and the residue washed with hot hexane (3 × 30 ml) to give 0.26 g (83%) of the 5-hydroxy-compound (Vf), mp 154-156°C (lit. mp 148-151°C [4]).

2-Methylthio-5-hydroxypyrimidine (X). A mixture of 10 ml of 2 M sulfuric acid and 1 g (5 mmoles) of the pyrimidine (VIII) [1] was boiled under reflux for 60 min, cooled to 20°C, and extracted with chloroform (10 × 30 ml). The chloroform extracts were combined, washed with water until neutral, dried over $MgSO_4$, and the chloroform removed to give 0.57 g (80%) of the pyrimidine (X), mp 166-168°C (from alcohol) (lit. mp 168-169°C [6]).

Obtained similarly from (VII) [1] was 2-chloro-5-hydroxypyrimidine (IX), yield 67%, mp 200-202°C (lit. mp 195-196°C [6]).

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