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SYNTHESIS OF N^6-ALKYL DERIVATIVES OF 2,6-DIAMINOPURINE

M. G. TAMARI and J. AWRUCH

Pharmaceutical Organic Technology, The Hebrew University School of Pharmacy, Jerusalem, Israel

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Abstract—An improved synthesis of N^6-alkyl derivatives of 2,6-diaminopurine (VI) starting from 2,4-diamino-5-nitroso-6-methylthiopyrimidine (IV) is described.

2,6-DIAMINOPURINE possess the amino feature of both guanine and adenine. This compound shows certain antimetabolitic effects.[1-3] The two amino groups have been substituted in attempts to increase the antimetabolitic character.

While the 6-amino group may be modified considerably with retention of biological activity, other changes in the purine nucleus have resulted in compounds, which are inactive in most of the test synthesis.[4,5]

The synthesis of compounds of this type—such as 2-amino-N^6 dimethylamino purine (II) have been achieved by heating the appropriate amine with 2-amino-6-methylthiopurine (I) in a sealed bomb at a high temperature.[6,*]

I II

We wish to report now a facile synthesis of N^6-alkyl derivatives of 2,6-diaminopurines which do not require such drastic conditions.

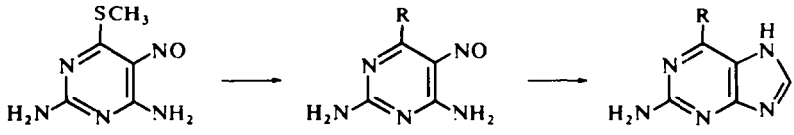
It is known, that while chlorobenzene is almost inactive toward nucleophilic attack, the introduction of a nitro group into the aromatic nucleus makes it highly reactive.[7] This activating effect is observed also in the pyrimidine series.[8,9] A similar influence is exerted by the carbalkoxy group in the proper position.[10,11] Moreoever, similar activation is observed, when the nitro- or nitroso-pyrimidine bears a methylthio group instead of a Cl atom.[12] We have used these nitroso-methyl-thiopyrimidines as starting materials in the synthesis of alkylaminopurines.[13]

Thus, compound IV[14] in an aqueous solution of the appropriate amine at atmospheric pressure gave V in high purity and yields.

The progress of the substitution-reaction can be followed conveniently by observing the change of the color from blue to rose-purple.[15]

The kinetics of this nucleophilic substitutions—as determined by spectrophotometric measurements—shows, that the displacement of the methylthio group in

* However, replacement of the chlorine atom in position 2 (III) with aqueous ammonia under the same conditions could not be accomplished.[6]



IV V VI

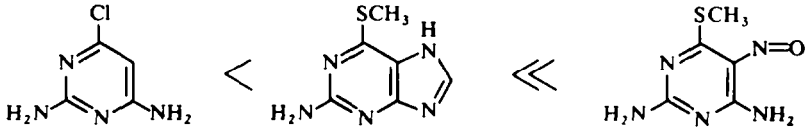
R: a = dimethylamino
b = pyrrolidino
c = piperidino
d = morpholino

R: a–d
as in V

position 6 (IV; *ortho* to the nitroso group) is approximately three times faster than that of the 2-methylthio-analog (*para*). This can be compared to the nitrochlorobenzene series, in which an *o/p* ratio of 36 was observed in nucleophilic substitution reactions.[7]

The nitrosopyrimidines (V, R: a–d) were reduced by sodium dithionite in formic acid to the corresponding aminopyrimidines, which were not isolated. The imidazole ring closure was affected with formamide. In some cases boiling with formic acid was sufficient for the closure.

The nucleophilic substitution of compound VII with dimethylamine has been described as requiring heating at 170° for 3 hr.[16]



VII I IV

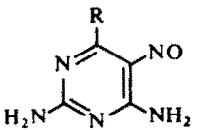
The same reaction with compound I takes 16 hr at 130°.[6] While admittedly these conditions may not be the mildest, they are by far more drastic than the ones required for the nucleophilic substitution described in the present paper (100° for 10–20 min). As I is known to be more reactive than VII, the following order of reactivities can be formulated:

$$\text{VII} < \text{I} \ll \text{IV}$$

Since the methylthio group is less reactive than the chlorine in position 6,* we can conclude that the imidazole ring possess electron-withdrawing property, similar, but much weaker to those of the nitroso group.

* This is indicated by the relative reactivities of 6-chloropurine and 6-methylthiopurine.[17]

TABLE 1. PHYSICAL PROPERTIES AND ANALYTICAL DATA OF 2,4-DIAMINO-5-NITROSO-6-ALKYLAMINOPYRIMIDINE (V)

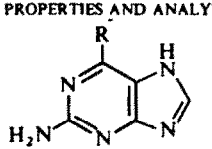


R	Yield %	M.p. °C	Formula	C % Calc	C % Found	H % Calc	H % Found	N % Calc	N % Found	λ_{max} (mμ) 0·1 HCl	R_F[b]	Fluorescence
Dimethylamino[a]	76	258/9	$C_6H_{10}N_6O$	39·6	39·6	5·5	5·6	46·2	46·2	281	0·71	Violet
Pyrrolidino	77	233/4	$C_8H_{12}N_6O$	46·2	46·1	5·8	5·8	40·4	40·7	319	0·74	Violet
Piperidino[a]	75	212/3	$C_9H_{14}N_6O$	48·7	48·8	6·3	6·0	37·8	37·6	281	0·75	Violet
Morpholino	87	225/6	$C_8H_{12}N_6O_2$	42·9	43·0	5·4	5·4	37·5	37·3	285	0·72	Violet

[a] Ref. 17.

[b] Solvent: Ethanol:DMF:Water = 60:20:20. All R_f values refer to theophylline (R_f = 0·75).

TABLE 2. PHYSICAL PROPERTIES AND ANALYTICAL DATA

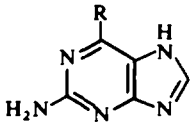


R	M.p. °C	Carbon % Calc	Carbon % Found	Hydrogen % Calc	Hydrogen % Found	Nitrogen % Calc	Nitrogen % Found	Recryst solv	Yield %	Method[b]
Dimethylamino[a]	>300	47·2	47·0	5·6	5·3	47·2	47·0	sublimation	68	A
Pyrrolidino	263/4	52·9	52·6	5·9	6·2	41·2	40·8	In KOH/AcOH	65	A
Piperidino	243/4	55·0	54·9	6·4	6·8	38·5	38·7	water	66	B
Morpholino	>300	49·1	49·0	5·5	5·6	38·2	38·0	ethanol/water	91	A

[a] Ref. 6.

[b] See Experimental section.

TABLE 3. SPECTROPHOTOMETRIC AND CHROMATOGRAPHIC DATA OF SOME 2-AMINO-6-ALKYLAMINOPURINES



R	0·1N HCl	0·1N NaOH	R_f in solvent[c]			Fluorescence
	λ_{max} (mμ)	λ_{max} (mμ)	A	B	C	
Dimethylamino[a]	228 256 282	226 289	0·67	0·78	0·70	blue
Pyrrolidino	228 255 283 290 sh[b]	224 290	0·75	0·72	0·79	violet
Piperidino	228 255 283 290 sh[b]	224 290	0·84	0·77	0·76	blue
Morpholino	234 257 286	232 290	0·60	0·75	0·69	blue

[a] Reference 6.

[b] sh = shoulder.

[c] Solvent A: Ethanol–Acetic Acid–Water = 85:5:10; B: Isopropanol–DMF–25% Ammonia = 65:25:10; C: Ethanol–DMF–Water = 60:20:20. All R_f values refer to theophylline (R_f = 0·75).

EXPERIMENTAL

Absorption spectra were measured in a CF "OPTICA" spectrophotometer. Paper chromatograms were developed by descending method using Whatman paper No. 1. Spots were located by their fluorescence under a Minerallight lamp emitting light about 254. All m.ps were taken on a Thomas–Hover m.p. apparatus and are uncorrected. The velocity of the nucleophilic substitution of the 2-methylmercapto-5-nitroso-pyrimidines and the 6-methylthio-5-nitrosopyrimidine was compared as follows: absorption spectra were measured in an Ultrascan double-beam recording spectrophotometer (Hilger and Walts Ltd).

Morpholine (0·5 ml) was added to each of two solns, one containing 10 ml of 2-methylmercapto-5-nitroso-2,6-diaminopyrimidine and the other containing 10 ml of 2,4-diamino-5-nitroso-6-methylthiopyrimidine, each soln being buffered to pH 9·2. The time of the reaction was 66 min and 22 min, respectively.

Starting materials. 2,4-Diamino-6-pyrimidinethiol was purchased from Fluka AG., Buchs. Known methods were used for the preparation of 2,4-diamino-5-nitroso-6-methylthiopyrimidine (IV).[16]

General procedure

Preparation of compound V (R: a–d). 2 g of compound IV were refluxed for 30 min with a 20% aqueous soln (80 cc) of the appropriate amine. On boiling, the starting material dissolved and the product began to recrystallize from the hot soln. After chilling V (R: a–d) was collected by filtration. V (R = d) recrystallized from boiling water. All other substances were chromatographically pure and were used in the next step. Samples for analyses were recrystallized from boiling water and dried at 100°/1 mm over P_2O_5.

The physical properties and analytical data of compound V (R: a–d) obtained are given in Table 1.

2-Amino-6-alkylaminopurines (VI, R : a–d)

Method A. To the appropriate nitrosopyrimidine (V, 0·013 mole) in 98–100% formic acid 2 equivs of $Na_2S_2O_4 \cdot 2H_2O$ were added at room temp. After 5 min stirring by means of magnetic stirrer, the discoloured soln was heated under reflux for 30 min. Formamide (40 cc) was added to the reaction mixture and the reflux continued for a further 2 hr. After chilling, the product was isolated by filtration and washed with ice–water. Samples for analysis were recrystallized from the appropriate solvent (Table 2) and dried at 100°/1 mm over P_2O_5.

Method B. This method is identical to the method A, but no formamide was added. After reduction of the nitroso-pyrimidine, the reaction mixture was heated under reflux for 24 hr. After cooling, the amorphous sulphur was separated by filtration and the filtrate was then evaporated to dryness under reduced press. The residue recrystallized from water.

Physical properties and analytical data of 2-amino-6-alkylaminopurines obtained are given in Tables 2 and 3.

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