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DEAMINATION, INVOLVING RING OPENING, IN REACTIONS OF 1-AMINOPURINIUM MESITYLENESULFONATES WITH METHANOLIC AMMONIA*

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Abstract. - On reaction of 1-aminopurinium mesitylenesulfonates with methanolic ammonia N-deamination occurs. For 1-amino-, 1-amino-8-(methylthio)-, 1-amino-8-phenyl-, 1-amino-2-methyl-, 1-amino-6-methyl- and 1-amino-8-phenyl-9-methylpurinium mesitylenesulfonate this reaction proceeds for at least 75% via ring opening as shown by the isolation of 1-^{15}N-labelled purines when ^{15}N-labelled methanolic ammonia was used. 1-Amino-9-methylpurinium mesitylenesulfonate gave N-deamination without ring opening. The reaction of 1-amino-6-(methylthio)purinium mesitylenesulfonate with methanolic ammonia involves, besides deamination, partial substitution of the methylthio group; no ring opening is involved. However, ring opening followed by substitution occurs in the reaction of 1-amino-2-(methylthio)purinium mesitylenesulfonate; the reaction proceeds via an adduct at position 2.

Recently we reported the preparation of a series of 1-aminopurinium salts by reaction of the corresponding purines with O-mesitylenesulfonylhydroxylamine (MSH).[1] For both 1,2- and 1,6-aminopurinium salts we have shown that reaction with methanolic ammonia or methylamine can lead to mono- and/or dideamination involving a ring opening mechanism (ANRORC-mechanism).[2,3] Like N-aminopyrimidinium salts,[4,5] also 1-aminopurines (or purinium salts) containing different substituents may be expected to undergo ring transformation reactions on treatment with nucleophiles. In this paper we present the results of our study on the reactions of these salts with methanolic ammonia.

RESULTS AND DISCUSSION

a. 1-Aminopurinium mesitylenesulfonates (1a-1g)

On reaction of the mesitylenesulfonate salts of 1-aminopurine (**1a**), 1-amino-8-(methylthio)purine (**1b**), 1-amino-8-phenylpurine (**1c**), 1-amino-2-methylpurine (**1d**), 1-amino-6-methylpurine (**1e**), 1-amino-9-methylpurine (**1f**) and 1-amino-8-phenyl-9-methylpurine (**1g**) with methanolic ammonia (for the reaction conditions see Table), deamination occurs leading to purine (**2a**, isolated yield 40%), 8-(methylthio)purine (**2b**, 25%), 8-phenylpurine (**2c**, 45%), 2-methylpurine (**2d**, 60%), 6-methylpurine (**2e**, 75%), 9-methylpurine (**2f**, 30%) and 8-phenyl-9-methyl-

* Dedicated to Prof.Dr. H. Wijnberg on occasion of his sixty-fifth birthday

purine (**2g**, 15%). It is interesting that **1f** and **1g** react much faster than **1a-1e**. No indication of the formation of other products could be found.

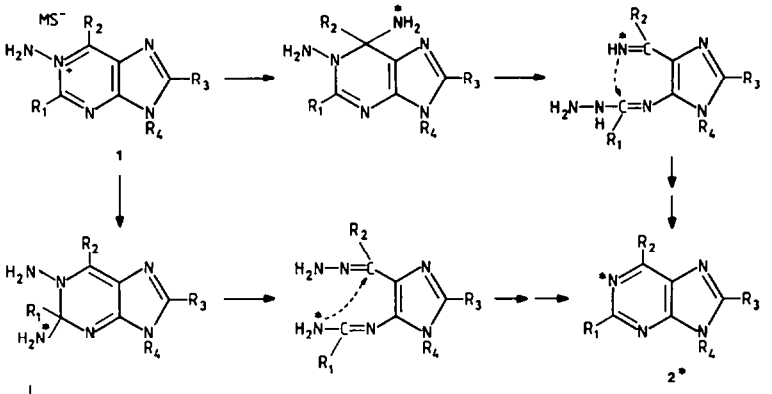
Table Reactions of 1-aminopurinium mesitylenesulfonates with methanolic ammonia (6.0% ^{15}N-labelled)

Mesitylenesulfonate salts of	reaction time (h)	reaction temp. (°C)	product	yield	^{15}%-content (%)[a]	ANRORC %
1-NH_2-purine (**1a**)	5	50	purine (**2a**)	40	5.6	95
1-NH_2-8-SCH_3-purine (**1b**)	5	50	8-SCH_3-purine (**2b**)	25	4.5	75
1-NH_2-8-C_6H_5-purine (**1c**)	17	100	8-C_6H_5-purine (**2c**)	45	5.0	85
1-NH_2-2-CH_3-purine (**1d**)	5	50	2-CH_3-purine (**2d**)	60	5.1	85
1-NH_2-6-CH_3-purine (**1e**)	17	100	6-CH_3-purine (**2e**)	75	5.7	95
1-NH_2-9-CH_3-purine (**1f**)	~ 0.02	20	9-CH_3-purine (**2f**)	30	0.0	0
1-NH_2-8-C_6H_5-9-CH_3-purine (**1g**)	~ 0.02	20	8-C_6H_5-9-CH_3-purine (**2g**)	15	5.7	95
1-NH_2-6-SCH_3-purine (**3**)	17	100	6-SCH_3-purine (**4**)	15	0.0	0
			6-OCH_3-purine (**9**)	20	0.0	0
			6-NH_2-purine (**6**)	50	5.9	0
1-NH_2-2-SCH_3-purine (**11**)	17	100	2-SCH_3-purine (**17**)	55	0.3	0
			2-NH_2-purine (**13**)	25	7.8	30

a. All experiments were carried out in duplicate; the accuracy of the mass spectroscopic measurements is ± 0.2%.

When these reactions were carried out with ^{15}N-labelled methanolic ammonia (containing 6.0% ^{15}N) in methanol, the products **2a-2e** and **2g** contained a considerable amount of ^{15}N-label (**2a***, 5.6% ^{15}N; **2b***, 4.5% ^{15}N; **2c***, 5.0% ^{15}N; **2d***, 5.1% ^{15}N; **2e***, 5.7% ^{15}N; **2g***, 5.7% ^{15}N). As an interesting contrast, **2f** was found to be unlabelled (see Table). Carrying out the reaction of **1a** into **2a** under more drastic conditions (17 h at 100°C instead of 5 h at 50°C) no difference was observed in the amount of ^{15}N-label incorporated into **2a***. These results show that, with the exception of **1f**, the N-deamination involves for the greater part (75-95%) a ring opening reaction with introduction of the ^{15}N-label into the pyrimidine nucleus. Direct nucleophilic attack of ammonia on the N-amino group only occurs in **1f** and plays only a minor role in the deamination of **1a-1e** and **1g**.[6] In order to ensure that the incorporation of the ^{15}N-label into the purine ring does not take place after the formation of the product, we reacted unlabelled **2a** and **2g** with ^{15}N-labelled methanolic ammonia. No incorporation of ^{15}N-label was found in recovered **2a** and **2g**. This result shows that in the reactions of **1a** into **2a** and/or **1g** into **2g** the ^{15}N-label was introduced during the deamination and not after product formation. The presence of a ^{15}N-label in the purine ring of **2a*** was confirmed by the ^{15}N NMR spectrum of **2a*** (measured in DMSO) showing only one signal at 276.7 ppm, which indicates that the label is present exclusively at N-1.[7] All these results clearly indicate that the reactions of **1a-1e** and **1g** with methanolic ammonia occur according to a process, involving a

ring opening/ring closure sequence [(ANRORC) mechanism] (Scheme I).



	R_1	R_2	R_3	R_4
a	H	H	H	H
b	H	H	SCH_3	H
c	H	H	C_6H_5	H
d	CH_3	H	H	H
e	H	CH_3	H	H
f	H	H	H	CH_3
g	H	H	C_6H_5	CH_3

Scheme I

Some remarks concerning the mechanism can be made.

Since the compounds **1a-1e** contain a hydrogen at position 9, it is likely that the N-aminopurinium cation is deprotonated and that the neutral species undergoes the addition.[3] This is in agreement with the observation that **1a-1e** react much slower than the 8-methyl derivatives **1f** and **1g**, which cannot be deprotonated.

It is not clear whether the initial addition of the ammonia takes place at C-2 or C-6.[2,3,8] Attempts to observe the formation of an adduct by ^{1}H-NMR spectroscopy failed. We observed only starting material (presumably the neutral species) and product. It cannot be excluded that also in **2d** and **2e** carrying a methyl group at C-2 and C-6 respectively, the addition occurs, at least partly, on the carbon, that carries the methyl group. There is ample evidence that the presence of a methyl group on a carbon atom adjacent to a ring nitrogen in an heteroaromatic compound does not prevent addition of ammonia to that position.[9] The fact that the 6-methyl derivative **1e** reacts much slower than the 2-methyl derivative **1d** can be considered as an indication that addition at C-6 is more favoured (although more direct N-deamination occurs in **1d** as compared with **1e**).

In Scheme I the addition at C-6 as well as C-2 has been pictured. It is evident that both reaction pathways lead to incorporation of the nitrogen of the ammonia into the ring at position 1. It is not clear why **1f** behaves differently. We want to remark that the reactions of 1-aminopurinium mesitylenesulfonates with ^{15}N-labelled methanolic ammonia provide a facile preparation of 1-^{15}N-labelled purines.

Attempts to convert **1a** into 1-methylpurine by treatment with methanolic methylamine were not successful; only purine was obtained. Thus, with methylamine a direct nucleophilic attack on the 1-amino group occurs, as also observed with the salt of 1,2-diaminopurine.[3] It was also impossible to convert **1a** into purine-1-oxide by reaction with hydroxylamine.[10]

b. 1-Amino-6-(methylthio)purinium mesitylenesulfonate (**3**)

Reaction of the purinium salt **3** with methanolic ammonia for 17 h at 100°C resulted in the formation of three products: adenine (**6**, yield 50%), 6-(methylthio)purine (**4**, 15%) and 6-methoxypurine (**9**, 20%) (Table I); in addition a trace amount of purine was found. In order to establish whether also in these conversions ring opening was involved, the reaction was investigated with ^{15}N-labelled methanolic ammonia (6.0% ^{15}N). We observed that **6*** contained 5.9% ^{15}N and that **4** and **9** were unlabelled (Table). The ^{15}N-label in **6*** was nearly exclusively present on the nitrogen of the exocyclic amino group, since hypoxanthine (**7**), obtained from **6*** by diazotization,[11] contained only 0.4% ^{15}N-label.

These results show that the presence of a leaving group on C-6 in a 1-aminopurinium salt directs the deamination and substitution in such a way that no ring opening is involved.

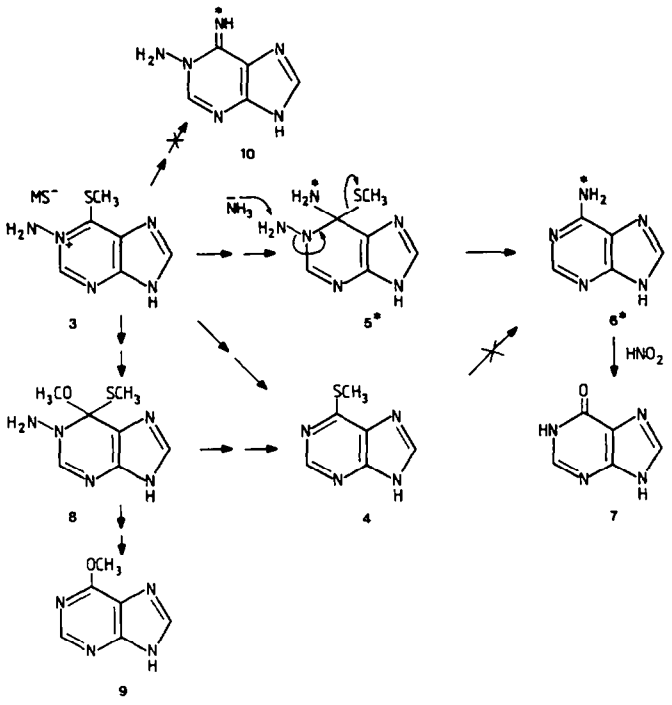
Considering the formation of **6** the following routes can be excluded (Scheme II): i) deamination of **3** into 6-(methylthio)purine (**4**) followed by aminolysis of **4** into **6**. However, heating of **4** with methanolic ammonia for 17 h at 100°C gave only a small percentage (less than 10%) of **6**; ii) aminolysis of **3** into 1-aminoadenine (**10**) followed by deamination at N-1. Reaction of **10** with methanolic ammonia indeed gave adenine (**6**), together with a considerable amount of purine. However, in previous experiments it has already been found that the adenine obtained from **10** contained a considerable amount of ^{15}N-label at N-1 when reacted with ^{15}N-labelled methanolic ammonia.[2] Since in the reaction of **3** with ^{15}N-labelled ammonia **6** is unlabelled at N-1, **10** cannot be an intermediate. Moreover, in the reaction of **3** with methanolic ammonia only traces of purine are found (see above).

Based on these data we suggest that the formation of **6** commences with the initial addition of ammonia to C-6 of the deprotonated species of **3**, yielding adduct **5**.[12] From adduct **5** compound **6** can be obtained by a process, involving N-deamination and loss of the methylthio group, without ring opening. An adduct could also be formed at C-2 of **3**,[2,3,8] but we have already indicated above that the difference in reaction velocity between **1d** and **1e** shows that the formation of an adduct at C-6 is more favourable.

The formation of 6-methoxypurine (**9**) does not involve adenine (**6**) or 6-(methylthio)purine (**4**); both **4** and **6** did not give **9** when reacted with methanolic ammonia for 17 h. This indicates that, analogous to the formation of **6**, **9** is formed via adduct **8**. It seems reasonable that compound **4** is also obtained from this adduct, although direct deamination of **3** into **4** cannot be excluded.

c. 1-Amino-2-(methylthio)purinium mesitylenesulfonate (**11**)

The reaction of **11** with methanolic ammonia gave as main product 2-(methylthio)-purine (**17**, yield 55%) together with 2-aminopurine (**13**, 25%). No 2-methoxypurine was found. When the reaction was carried out with 6.0% ^{15}N-labelled methanolic



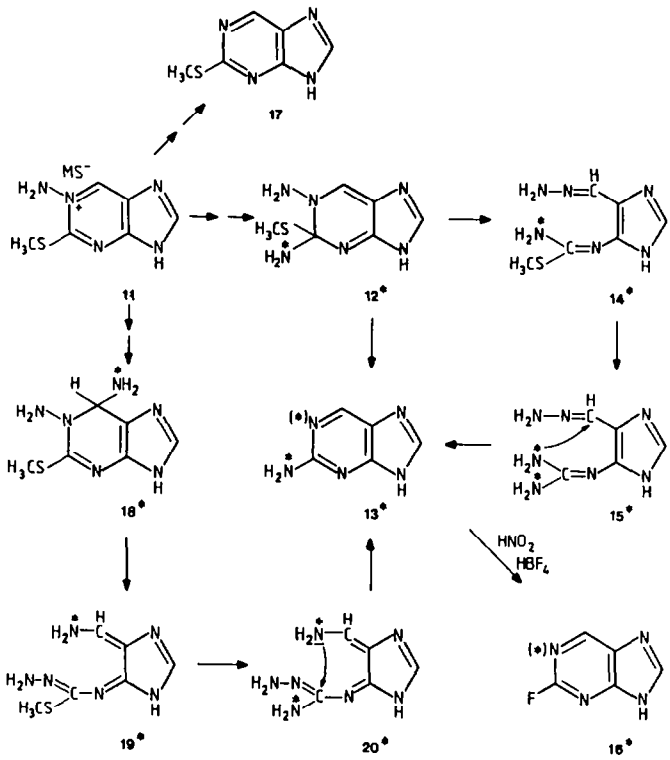
Scheme II

ammonia we found that **17** was practically unlabelled, but that **13** contained 7.8% ^{15}N-label! (see Table). This remarkable result indicates that compound **13*** must be labelled (partially) at two nitrogen positions. Diazotization of **13*** in fluoroboric acid[13] gave 2-fluoropurine (**16***) containing 1.8% ^{15}N-label. We conclude that **13*** contains 6.0% ^{15}N-label at the nitrogen of the exocyclic amino group and 1.8% ^{15}N-label at a nitrogen in the ring, presumably N-1. For the formation of **13** two routes can be excluded (Scheme III):

i) deamination of **11** into **17** followed by aminolysis of **17** into **13**; on treatment of **17** with methanolic ammonia for 17 h at 100°C no **13** was obtained; ii) aminolysis of **11** into 1,2-diaminopurine followed by deamination at N-1. Reaction of 1,2-diaminopurine with methanolic ammonia gave not only 2-aminopurine but also purine, which was not found in the reaction of **11** with methanolic ammonia.[2]

Therefore we have to assume that a similar mechanism operates as observed in the reaction of **3**, however, the initial addition of ammonia takes place to C-2 and not to C-6, giving **12**.

By N-deamination and loss of the methylthio group **13** could be obtained from **12**. However, the 2-aminopurine (**13***) formed via this route should only be labelled in the exocyclic amino group. As mentioned before **13*** did not only contain the ^{15}N-label at the exocyclic amino group, but also at N-1. This result shows that in the formation of a part of **13*** the (ANRORC) mechanism has to be operative. We suggest that adduct **12*** undergoes ring opening into **14***, in which the methylthio group can easily be displaced by an amino group to give **15***. Ring closure of **15*** with loss of the hydrazino group gives **13***, labelled at N-1 as well as at the exocyclic amino group. Ring closure of **14*** before the displacement of the



Scheme III

methylthio group seems not to occur since it would lead to ^{15}N-labelled 2-(methylthio)purine which compound is actually not formed.

Another mechanism that may lead to doubly labelled **13** involves the intermediacy of C_6-adduct **18***.[14] Ring opening of **18*** gives **19***, in which the methylthio group can easily be displaced by an amino group to give **20***. Ring closure of **20*** with loss of the hydrazino group also leads to doubly labelled **13***. Ring closure of **19*** by elimination of the methylthio group before the formation of **20*** seems not to occur since it would lead to 2-hydrazinopurine which is not found.

EXPERIMENTAL

^1H-NMR spectra were obtained with a Varian EM390 using Me_4Si as internal standard. ^{13}C-NMR spectra were obtained on a Bruker CXP-300 spectrometer operating at 75.460 MHz. The spectra were run with sweep width 15 000 Hz, using Quad detection mode with 8K data (Hz/pt 3.7), pulse width 12 μs and pulse delay 5 s. tMS was used as internal reference. ^{15}N-NMR-spectra were obtained similarly operating at 30.408 MHz.

As internal reference an internal cap. o.d. 2 mm was used containing CD_3NO_2 and ca 1% enriched $CH_3{}^{15}NO_2$. The samples were run in 10 mm o.d. tubes.

Mass spectra and ^{15}N contents were determined on an AEI MS-902 mass spectrometer.

The preparation of all the 1-aminopurinium mesitylenesulfonates used in this study is described before,[1] except the salt of 1-amino-6-methylthiopurine which

was prepared similarly (yield 64%, m.p. 151-152°C), anal. calcd for $C_{15}H_{19}N_5O_3S_2$; C, 47.22; H, 5.02. Found: C, 47.12; H, 4.75. ^{1}H-NMR ($CDCl_3/CD_3OD$) δ 9.04 (H-2), 8.56 (H-8) and 3.51 (SCH_3). ^{13}C-NMR (DMSO-d6) δ 148.4 (C-2), 149.0 (C-4), 129.1 (C-5), 155.0 (C-6), 151.3 (C-8), 30.1 (SCH_3).

The reactions with methanolic ammonia were carried out as described previously;[2] conditions and the yields are summarized in the Table.

The diazotizations of adenine (**6**) into hypoxanthine (**7**) and of 2-aminopurine (**13**) into 2-fluoropurine (**16**) were carried out with sodium nitrite in sulphuric acid[11] and fluoroboric acid[13] respectively as described in the literature.

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15. On reaction with methanolic ammonia (17 h, 100°C) 2-hydrazinopurine is converted into purine, which is not found in the reaction of **11**.[2]