# Thermal Decomposition of Quaternary Hypoxanthinium Salts and Related Purines

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Thermal degradation of quaternary hypoxanthinium salts was achieved by heating their solutions in dimethylformamide. 1,3-Dialkylhypoxanthinium bromides or iodides lose the 3-substituent as alkyl halide. The latter then attacks the imidazole ring at N-7 or N-9. Thermolysis of 1,3-dimethyl-6,8-dioxotetrahydropurinium iodide proceeds along either of two pathways: (i) loss of the 3-methyl group as methyl iodide, leading to 7,9-dihydro-1-methylpurine-6,8-(1*H*)-dione; or removal of hydrogen iodide to give the corresponding betaine, which is methylated at N-9 to give the 1,3,9-trimethyl-6,8-dioxotetrahydropurinium salt. The latter in turn decomposes to 7,9-dihydro-1,9-dimethylpurine-6,8(1*H*)-dione. Similarly 7,9-dimethylhypoxanthinium iodide (16) is degraded mainly, by loss of methyl iodide, to 9-methylhypoxanthine, accompanied by a small amount of the 7-methyl isomer. Compound (16) can also lose hydrogen iodide to give the corresponding betaine, which suffers methylation at N-1 to give the 1,7,9-trimethylhypoxanthinium salt. The latter again undergoes thermolysis to give a mixture of 1,7- and 1,9-dimethylhypoxanthine.

THERMAL decomposition of quaternary benzyl derivatives of hypoxanthine has been studied by Montgomery and his co-workers.[1] 7,9-Dibenzylhypoxanthinium bromide, upon prolonged heating in dimethylacetamide, yielded mainly 9-benzylhypoxanthine, with small amounts of the 1,7- and 1,9-dibenzyl derivatives. Similarly, 1,3-dibenzylhypoxanthinium bromide gave as acid leads exclusively to 1-benzylhypoxanthine, because the benzyl bromide liberated separates from the aqueous solution as an organic phase and is thus 'inactivated.'[4]

We have investigated whether quaternary *N*-methylhypoxanthinium salts suffer similar de- and transalkylations. The results shed some light on the mechanism of these reactions.

TABLE 1

Thermolysis of *NN'*-dialkylhypoxanthinium salts and betaines

| Compd. | Substituents [a] | Procedure [b] | Me substituents in products [c] | Relative proportions of products [d] |
|---|---|---|---|---|
| (A) 1,3-Dialkylhypoxanthinium salts and betaines | | | | |
| (1) | 1,3-$Me_2$ | A | 1; 1,7; 1,9; 1,7,9 | 3 : 2 : 2 : 1 |
| (2) | 1,3,8-$Me_3$ | A | 1,8; 1,7,8; 1,8,9; 1,7,8,9 | 8 : 5 : 5 : 2 |
| (3) | 1,3-$Me_2$-8-Ph | A | 1; 1,7; 1,9 | 30 : 3 : 2 |
| (4) | 1,3-$Me_2$-8-SMe | A | 1; 1,7; 1,9 (+ traces of 1,3,7) | 10 : 1 : 1 |
| (5) | 1-$PhCH_2$-3,8-$Me_2$ | A | 8 (+ traces of 7,8 and 8,9) | |
| (10) | 1,3-$Me_2$-8-(:O) | A | 1; 1,9 | 4 : 1 |
| | | B | 1; 1,9 | 1 : 3 |
| (10a) | 1,3-$Me_2$-8-(:O)(betaine) | C | 1,9; small amounts of 1,3,9 [e] | |
| | | B | 1,9; 1,7,9 | 3 : 1 |
| (B) 7,9-Dimethylhypoxanthinium iodides and betaines | | | | |
| (16) | 7,9-$Me_2$ | A | 9; 7,9 (small amounts of 7; + traces of 1,7 and 1,9) | 1 : 1 |
| (16a) | 7,9-$Me_2$ (betaine) | B, C | 1,7,9 | >90% |
| (21) | 1,7,9-$Me_3$ | A | 1,9; 1,7 | 2 : 1 |
| (22) | 1,7,8,9-$Me_4$ | A | 1,7,8; 1,8,9; 1,7,8,9 | 1 : 2 : 4 |

[a] All quaternary derivatives were used as iodides; only compound (5) was used as bromide. [b] A, a solution of the quaternary salt (0.2 g) in dimethylformamide (3 ml) was refluxed for 5 h; B, A solution of the purine (0.2 g) in dimethylformamide (10 ml) was refluxed with 50 equiv. of methyl iodide for 5 h; C, a solution of the betaine (0.1 g) in dimethylformamide (10 ml) and 50 equiv. of methyl iodide was warmed on a water-bath for 4 h. [c] The betaines did not yield the products shown in the column when thermolysed in the absence of methyl iodide. [d] Approximate determination by integration of the areas underneath the n.m.r. signals. [e] 1,3,9-Trimethyl-6,8-dioxotetrahydropurinium cation (13) is recognised in the mixture with (6a) and (12) by its characteristic n.m.r. signals.[6]

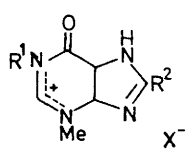
main product 1-benzylhypoxanthine, with small amounts of the latter further substituted at N-7 and N-9. Miyaki *et al.* have shown that the transfer of benzyl groups in certain adenine derivatives is an intermolecular process, involving elimination of benzyl bromide and attack by this species at nucleophilic sites.[2,3] This agrees with the observation that thermal decomposition of 1,3-dibenzylhypoxanthinium bromide in 48% hydrobromic

Table 1A shows that in a variety of 1,3-dimethylhypoxanthinium salts only the 3-alkyl group is eliminated upon heating in dimethylformamide. Even in the 1-benzyl-3,8-dimethyl derivative (5), only the 3-methyl substituent is removed, although in quaternary ammonium salts benzyl is usually eliminated in preference to methyl.

The 3-methyl group may be shifted to the imidazole ring, substituting positions 7 and 9 to about the same extent [see compounds (1)—(4)]. However when

[1] J. A. Montgomery, K. Hewson, S. J. Clayton, and H. J. Thomas, *J. Org. Chem.*, 1966, **31**, 2202.
[2] M. Miyaki, K. Iwase, and B. Shimizu, *Chem. and Pharm. Bull.* (*Japan*), 1966, **14**, 87.
[3] B. Shimizu, and M. Miyaki, *Tetrahedron Letters*, 1965, 2059.
[4] Z. Neiman, and F. Bergmann, *Israel J. Chem.*, 1968, **6**, 9.

position 8 bears a bulky substituent like methylthio (4) or phenyl (3), alkylation at N-7 or N-9 becomes more difficult and loss of methyl halide is predominant.

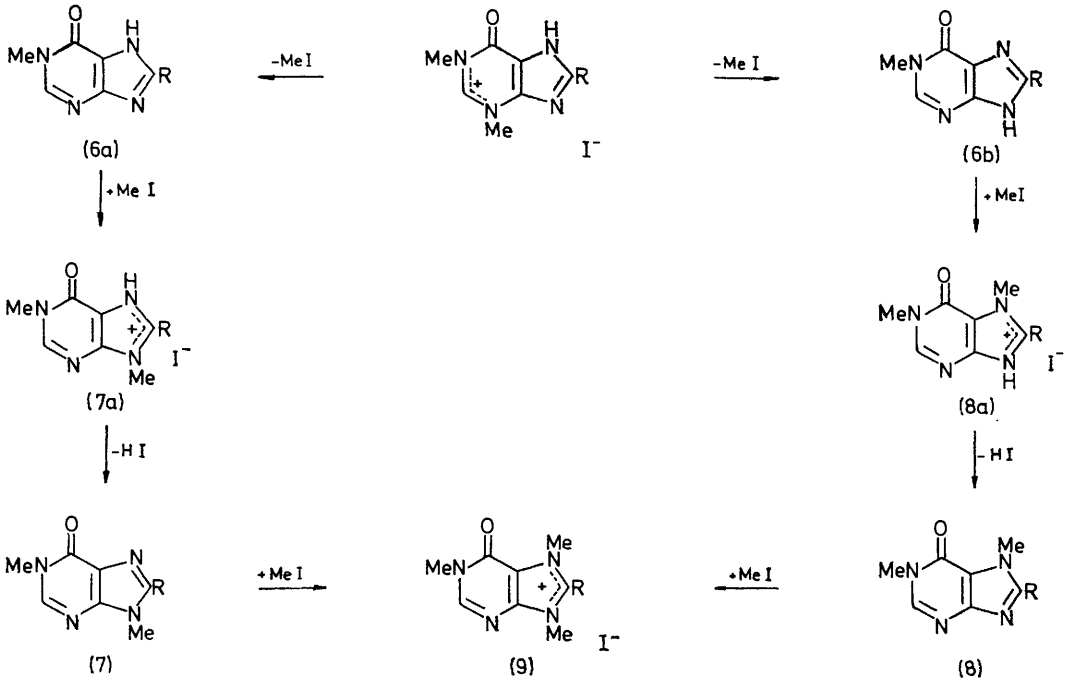


| | $R^1$ | $R^2$ | X |
|---|---|---|---|
| (1) | Me | H | I |
| (2) | Me | Me | I |
| (3) | Me | Ph | I |
| (4) | Me | MeS | I |
| (5) | $PhCH_2$ | Me | Br |

The occurrence of an intermolecular transfer of methyl groups can be deduced from the observation that 1,3-dimethyl- (1) and 1,3,8-trimethyl-hypoxanthinium salts (2) yield a certain amount of 1,7,9-trimethylhypoxanthinium salt (9; R = H or Me) and 1,3-dimethyl-8-methylthiohypoxanthinium salt (4) yields traces of neutral *NN'*-dimethylhypoxanthines (7) and (8), which are again available for methylation to give (9). This Scheme is based on the results of alkylation of pre-formed (6; R = H), (19), and (20).[5]

However the same mechanism cannot apply to the 1,3-dimethyl-6,8-dioxotetrahydropurinium salt (10). Here, thermolysis yields 7,9-dihydro-1-methylpurine-6,8(1*H*)-dione (11) as main product (*ca.* 80%). It was shown previously that this compound is attacked by methyl iodide at N-3 (Scheme 2), since position 9 is blocked.[6] Thus the formation of *ca.* 20% of the 1,9-dimethyl derivative (12) cannot take place along the path (10) ⟶ (11) ⟶ (12).

Removal of the 9-proton cannot be achieved with the neutral dione (11). Therefore the possibility has to be considered that the quaternary salt (10) may in part suffer thermal dissociation into hydrogen iodide and the



SCHEME 1

the corresponding 1,3,7-trimethyl derivative (see Table IA).

We stress that the zwitterions corresponding to the hypoxanthinium salts in Table 1 do not yield any new purines under the conditions of thermolysis used for the quaternary salts.

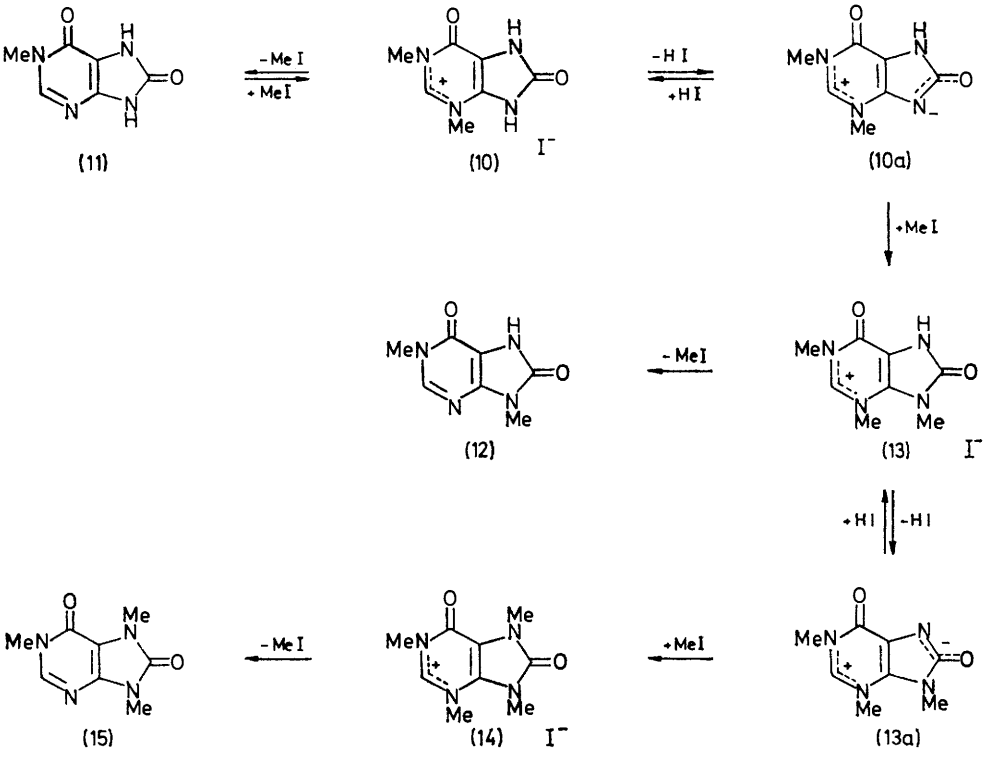
In the first step of the process (Scheme 1) the quaternary starting material yields the uncharged 1-methylhypoxanthine (6). The latter may be attacked in either of its tautomeric forms (6a or b) to yield amidinium-like salts (7a) and (8a).[5] Further electrophilic attack on the latter is possible if, at the temperatures used, dissociation takes place into HI and the betaine (10a). The latter could serve as substrate for electrophilic alkylation by methyl iodide. Indeed refluxing a solution of pre-formed (10a) in dimethylformamide with 50 equiv. of methyl iodide produced a high yield of the 1,9-dimethyl derivative (12) and a smaller amount of 7,9-dihydro-1,7,9-trimethylpurine-6,8(1*H*)-dione (15) (ratio 3 : 1) (Table 1A). When the reaction was carried out at 90 °C, it was possible to identify during the initial stages the 1,3,9-trimethyl derivative (13). This compound disappeared gradually to yield (12) and (15). However, the 1-methyl derivative (11) was absent throughout the reaction period. We thus propose that formation of (12) takes place along the

[5] U. Reichman, F. Bergmann, and D. Lichtenberg, *J.C.S. Perkin I*, 1973, 2647.

[6] M. Rahat, F. Bergmann, and I. Tamir, *J.C.S. Perkin I*, 1974, 2229.

path (10a) ⟶ (13) ⟶ (12) (Scheme 2). Under the more drastic conditions (reflux), the intermediate (13) is unstable and therefore could not be identified beyond doubt.

These results show that conversion of the 1,3-dimethyl derivative (10) into the 1,9-dimethyl isomer (12) could be achieved by intermolecular alkylation. The simultaneous formation of the 1-methyl (11) and the 1,9-dimethyl derivative (12) during thermolysis of (10) can be explained as follows (Scheme 2). Part of (10) dissociates into methyl iodide and (11), and another




SCHEME 2

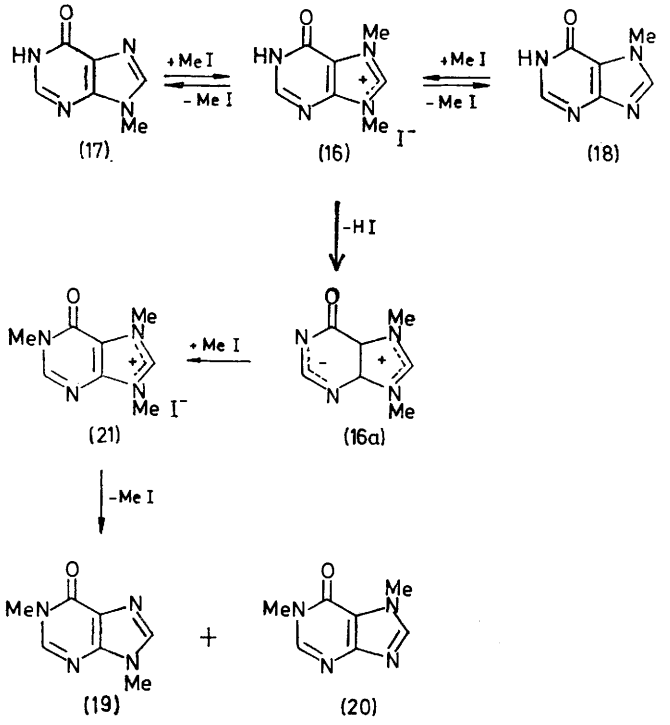
(smaller) part into hydrogen iodide and the betaine (10a). The latter is then attacked by methyl iodide to give the 1,3,9-trimethyl derivative (13), which serves as precursor of (12). Therefore the 3 : 1 ratio of (11) to (12) may represent the relative contributions of the two thermal dissociation processes. However since the reaction (10) ⟶ (11) is reversible,[6] only part of the methyl iodide that becomes available during thermolysis of (10) may be used for alkylation of (10a), and this fact may also contribute to the low yield of (12). This explanation is supported by the observation that when a solution of (10) in dimethylformamide is heated with addition of external methyl iodide, the yield of the 1,9-dimethyl derivative (12) is increased considerably (see Table 1A). In the presence of an excess of methyl iodide, most of the 1-methyl derivative (11) is converted back into (10). Therefore the proportion of (10) splitting off hydrogen iodide to yield the betaine (10a) slowly increases with time.

In an analogous way we may explain the formation of the 1,7,9-trimethyl derivative (15), which represented about 25% of the products from the reaction of (10a) with an excess of methyl iodide (see above). Alkylation at N-7 requires dissociation of the 7-NH group in (13). The p$K$ for the transformation of the cation (13) into the zwitterion (13a) is 2.4.[6] Therefore thermal dissociation of (13) into hydrogen iodide and the betaine (13a) should proceed as smoothly as the conversion of (10) into (10a) (p$K$ 2.8). Although the 1,3,7,9-tetramethyl intermediate (14) was not identified, we assume the reaction path (13) ⟶ (13a) ⟶ (14) ⟶ (15) (see Scheme 2).

Thermolysis of 7,9-dimethylhypoxanthinium iodide (16) in boiling dimethylformamide produces mainly 9-methylhypoxanthine (17), together with a small amount of the 7-methyl isomer (18) (Table 1B). These results parallel the observations with 7,9-dibenzylhypoxanthinium bromide.[1] Transfer of a methyl group to position 1 to form 1,9- (19) and 1,7-dimethylhypoxanthine (20) (Scheme 3) occurs only to a small extent. Similar results were obtained with the 1,8-dimethyl homologue (22) of (16) (see Table 1B).

The formation of compounds (19) and (20) cannot result from methylation of (17) and (18), because methyl iodide converts both these purines into (16).[5] Thus alkylation at N-1 must take place before demethylation in the imidazole ring. For N-1 alkylation it is necessary to remove the 1-proton by conversion of (16) into its betaine (16a). The latter is attacked by methyl iodide

at N-1 [formation of the 1,7,9-trimethylhypoxanthinium salt (21)], position 3 being much less accessible because




SCHEME 3

of the steric influence of the 9-methyl substituent. Thermolysis of (21) then yields the 1,9- (19) and the 1,7-dimethyl derivative (20), a process analogous to thermal degradation of (16) (Scheme 3).

This mechanism is strongly supported by the results obtained upon exposure of pre-formed (16a) to a large excess of methyl iodide. At 90 °C as well as at reflux temperature, the 1,7,9-trimethyl derivative (21) is formed exclusively. When a solution of (21) in dimethylformamide is refluxed in the absence of methyl iodide the compound decomposes to give a 2 : 1 mixture of (19) and (20). If methyl iodide is present, both these hypoxanthines are realkylated to give (21).[5]

*N.m.r. Spectra* (*Table* 2).—As shown previously,[7] cation formation in the pyrimidine ring of hypoxanthines shifts the 2-H signal downfield by *ca.* 0.8—1 p.p.m. Table 2 shows that the $\delta_{2-H}$ values of the cations of 3-benzyl-8-methylhypoxanthine and of the fixed cations (2), (5), and 3-benzyl-1,8-dimethylhypoxanthinium are >9. Two types of 8-methyl signal in cations of hypoxanthines are observed. If the positive charge is in the imidazole ring, as in 1,8-dimethyl-, 1-benzyl-8-methyl-, and 1,7,8,9-tetramethyl-hypoxanthinium cations, $\delta_{8-Me}$ is 2.9—3.0 (Table 2). On the other hand, for pyrimidinium cations this value is 2.6—2.8 (see entries 3—6 in Table 2).

## EXPERIMENTAL

Analyses and paper chromatographic data for all new purines are available as Supplementary Publication No. SUP 21600 (5 pp.).†

*Purines.*—The following purines were synthesised according to reported procedures: compound (1);[8] 1-methylhypoxanthine;[9] 1,7-[10] and 1,9-dimethylhypoxanthine;[11] 1,7,9-trimethylhypoxanthinium iodide;[5] 1,3-dimethyl-8-phenylhypoxanthinium iodide;[12] 1,7- and 1,9-dimethyl-8-phenylhypoxanthine;[13] all derivatives mentioned of 8-methylthiohypoxanthine;[14] all derivatives mentioned of purine-6,8-dione.[6]

TABLE 2

Physical properties of purines

| Entry no. | | $\lambda_{max.}$/nm [a] (log ε) | Solvent | $\delta_H$ 2-H [b] | N·$CH_3$ [c] | 8-$CH_3$ | $CH_2$ | $C_6H_5$ |
|---|---|---|---|---|---|---|---|---|
| (A) Neutral hypoxanthines | | | | | | | | |
| 1 | 1,8-$Me_2$ | 253 (3.98) | TFA [d]–$D_2O$ | 8.55 | 3.79 | 2.95 | | |
| 2 | 1-$PhCH_2$-8-Me | 255 | TFA | 8.72 | | 2.99 | 5.45 | 7.37 |
| 3 | 3-$PhCH_2$-8-Me | 266 (4.12) | TFA–$D_2O$ | 9.12 | | 2.70 | 5.70 | 7.45 |
| (B) Quaternary hypoxanthinium salts | | | | | | | | |
| 4 | 1,3,8-$Me_3$ (2) | 266 (3.88) | TFA–$D_2O$ | 9.52 | (1) 3.94, (3) 4.27 | 2.82 | | |
| | | | $D_2O$, pH 7 [e] | 9.50 | (1) 4.02, (3) 4.16 | 2.72 | | |
| 5 | 1-$PhCH_2$-3,8-$Me_2$ (5) | 259 † (4.17), 255 ‡ (4.12) | $D_2O$, pH 7 [e] | 9.61 | 4.09 | 2.59 | 5.39 | 7.40 |
| 6 | 3-$PhCH_2$-1,8-$Me_2$ | 266 (3.96) | TFA–$D_2O$ | 9.39 | 3.83 | 2.72 | 5.73 | 7.52 |
| 7 | 1,7,8,9-$Me_4$ | 254 (3.98) | $D_2O$, pH 7 [e] | 8.63 | (1) 3.98, (7) 4.26, (9) 4.01 | 2.92 | | |
| (C) Xanthines | | | | | | | | |
| 8 | 3-$PhCH_2$-8-Me-2-thio | 296 (4.25) | TFA | | | 2.87 | 5.87 | 7.37 |

[a] In methanol; for compound (5) only aqueous solutions of pH 1 (†) and 8 (‡) were used. [b] For entries 4—6, in which rapid H–D exchange takes place, the 2-H δ value was determined in $H_2O$. [c] Numbers in brackets indicate assignment of the signals to individual *N*-methyl groups. [d] Trifluoroacetic acid. [e] Phosphate buffer of pH 7 was added.

† For details of Supplementary Publications see Notice to Authors No. 7, *J.C.S. Perkin I*, 1974, Index issue.

[7] D. Lichtenberg, F. Bergmann, and Z. Neiman, *Israel J. Chem.*, 1972, **10**, 805.
[8] D. Lichtenberg, and F. Bergmann, *J.C.S. Perkin I*, 1973, 789.
[9] G. B. Elion, *J. Org. Chem.*, 1962, **27**, 2478.
[10] E. Fisher, *Ber.*, 1898, **31**, 439.
[11] E. G. Krebs and E. R. Norris, *Arch. Biochem. Biophys.*, 1949, **24**, 49.
[12] Z. Neiman, *J. Chem. Soc.* (*C*), 1970, 91.
[13] Z. Neiman, F. Bergmann, and D. Lichtenberg, *J. Chem. Soc.* (*C*), 1971, 1822.
[14] F. Bergmann, G. W. Chen, and M. Rahat, *J.C.S. Perkin I*, 1976, 90.

The synthesis of 6-amino-3-benzyl-5-formamidopyrimidin-4(3*H*)-one will be described separately.

1,3,8-*Trimethylhypoxanthinium Iodide* (2).—A solution of 3,8-dimethylhypoxanthine [15] (0.5 g) in acetonitrile (20 ml) and methyl iodide (2 ml) was kept at 60—65 °C for 90 h. The *precipitate* (2) was filtered off and washed with acetone and afforded plates (50%), m.p. 242° (from ethanol).

The betaine of (2) was prepared by adding silver acetate (0.17 g) in water (20 ml) to a solution of (2) (0.3 g) in water (3 ml). Silver iodide was filtered off and the filtrate lyophilised.

1-*Benzyl*-3,8-*dimethylhypoxanthinium Bromide* (5).—A suspension of 3,8-dimethylhypoxanthine (0.5 g) in benzyl bromide (0.5 g) and acetonitrile (250 ml) was refluxed for 20 h. The clear solution was reduced to half its volume and cooled to deposit the quaternary bromide (0.8 g, 80%), which afforded *needles*, m.p. 240° (from butan-1-ol).

1-*Benzyl*-8-*methylhypoxanthine*.—An intimate mixture of 6-amino-3-benzyl-5-formamidopyrimidin-4(3*H*)-one (0.1 g), acetamidine hydrochloride (0.1 g), and anhydrous sodium acetate (0.2 g) was heated to 190 °C for 15 min. The resulting solid was washed with a few drops of water and the insoluble portion was recrystallised from boiling water. The product was identical with the principal product obtained by thermolysis of (5) (see Table 1A).

3-*Benzyl*-1,8-*dimethylhypoxanthinium Iodide and* 1,8-*Dimethylhypoxanthine*.—(a) 3-*Benzyl*-8-*methyl*-2-*thioxanthine*. An intimate mixture of 5,6-diamino-1-benzyl-2-thiouracil [16] (2.5 g), acetamidine hydrochloride (2 g), and anhydrous sodium acetate (4 g) was heated to 150 °C for 5 min. The solid was triturated with N-sodium hydroxide, the mixture was filtered, and the filtrate was neutralized with glacial acetic acid. The product formed *needles* (70%), decomp. >300° (from acetic acid).

(b) 3-*Benzyl*-8-*methylhypoxanthine*. A solution of the foregoing thione (1.5 g) in concentrated ammonia (150 ml) was stirred with Raney nickel (4.5 g) and refluxed for 2 h. The filtrate was treated with charcoal and filtered again, and the solution was neutralised with acetic acid, giving *cubes* (60%), decomp. >300° (from dilute acetic acid).

(c) 3-*Benzyl*-1,8-*dimethylhypoxanthinium Iodide*.—A suspension of the foregoing hypoxanthine (0.5 g) in acetonitrile (100 ml) and methyl iodide (1 ml) was stirred at 60 °C for 72 h. The starting material dissolved progressively while the product crystallised out. The latter was filtered off, washed with acetone, and recrystallised from propan-1-ol to give *needles* (55%), m.p. 221°.

(d) 1,8-*Dimethylhypoxanthine Hydrobromide*.—A solution of the foregoing iodide (1 g) in 48% hydrobromic acid (30 ml) was kept at room temperature for 3 days. The solution was then brought to dryness *in vacuo* and the residue triturated first with methanol and then (after evaporation of the latter) with ether–acetone, giving *needles* (100%), decomp. >300° (from acetic acid–butyl acetate).

7,9-*Dimethylhypoxanthinium Iodide* (16).—The following method proved superior to the synthesis described in the literature.[12] A suspension of hypoxanthine (1 g) in dimethylformamide (10 ml) and methyl iodide (3 ml) was stirred at 60 °C for 1 h; a clear solution was obtained. Addition of an excess of ether precipitated compound (16). The ether was decanted, and this procedure was repeated several times. Finally the syrupy residue was triturated with acetone. Recrystallisation from ethanol gave plates (1 g, 50%), m.p. 257° (decomp.), identified by conversion into the corresponding betaine.[17]

1,7,8,9-*Tetramethylhypoxanthinium Iodide*.—A solution of 3,8-dimethylhypoxanthine (0.5 g) in dimethylformamide (5 ml) and methyl iodide (1 ml) was heated to reflux for 4 h, then evaporated to dryness *in vacuo*, and the residue was treated with acetone. The product afforded *needles* (85%), m.p. 262° (from butan-1-ol).

[5/1353 *Received*, 7*th July*, 1975]

[15] F. Bergmann and M. Tamari, *J. Chem. Soc.*, 1961, 4468.
[16] D. J. Brown and N. W. Jacobsen, *J. Chem. Soc.*, 1965, 1175.
[17] J. W. Jones and R. K. Robins, *J. Amer. Chem. Soc.*, 1962, **84**, 1914.