Tetrahedron Letters, Vol.32, No.1, pp 97-106, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

SYNTHESIS OF THE SEA ANEMONE PURINE CAISSARONE

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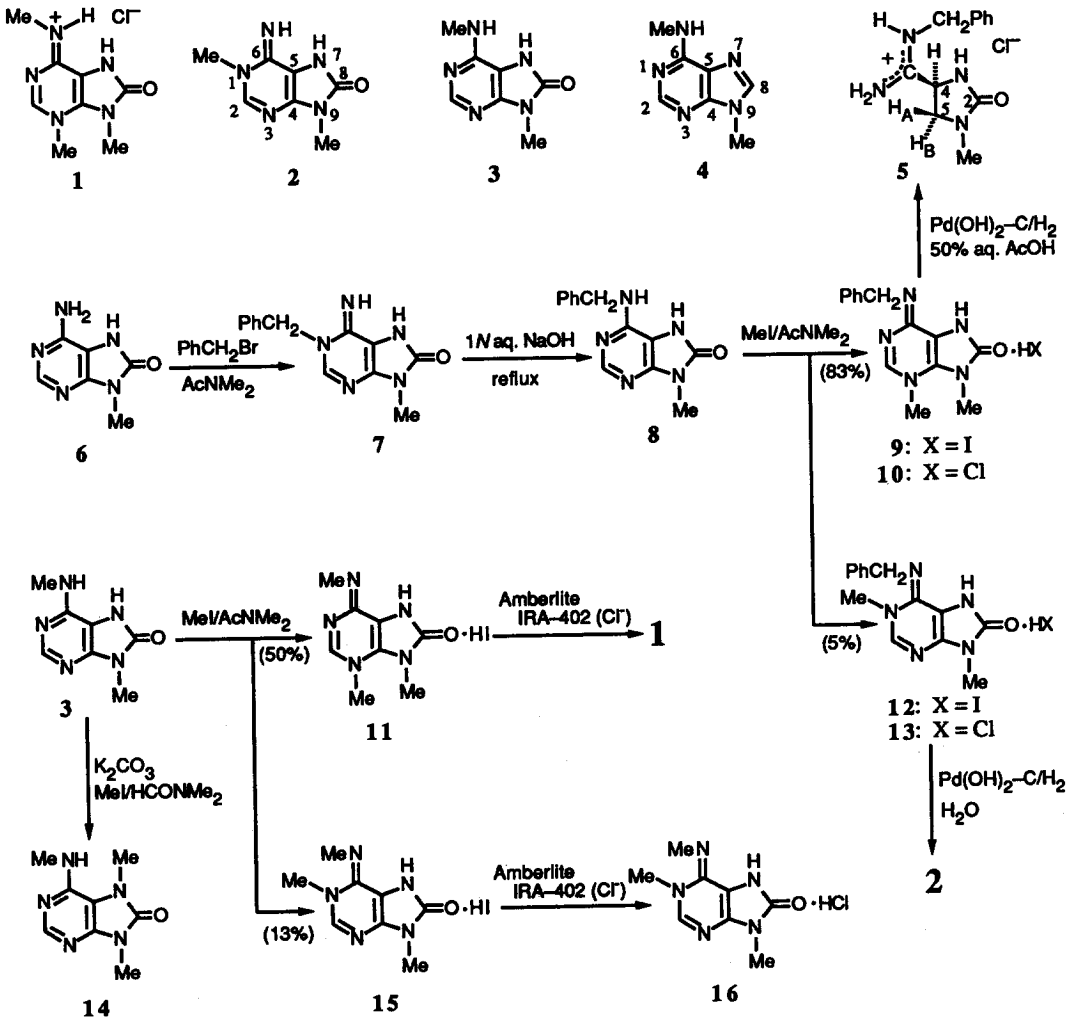
Summary: On the basis of a methylation study of N^6-benzyl-9-methyl-8-oxoadenine (**8**), the first synthesis of caissarone hydrochloride (**1**) has been achieved via a two-step route including methylation of the N^6-methyl analogue (**3**).

Caissarone is a novel 8-oxopurine isolated by Zelnik *et al.* as its hydrochloride (**1**) from the sea anemone *Bunodosoma caissarum* Correa 1964.[1] Caissarone hydrochloride (**1**) induces various anomalies in sea urchin egg development,[2] and its chemical structure has been established by spectroscopic measurements and X-ray diffraction analysis.[1] Our recent success[3] in synthesizing the marine sponge base 6-imino-1,9-dimethyl-8-oxopurine (**2**) as well as the N^6,9-dimethyl isomer (**3**)[3,4] led us to design a concise synthetic route to **1** from **3** in the present study.

El'tsov *et al.* reported that treatment of N^6,9-dimethyladenine (**4**) with MeI in $HCONMe_2$ at 100—105°C (in a sealed vessel) for 10 min resulted in monomethylation on N(1), N(3), and N(7) with a 51 : 30 : 19 selectivity.[5] In view of such a second preference for methylation at the 3-position, we first checked the regioselectivity in methylation of the N^6-benzyl analogue **8** in the 8-oxoadenine series. For preparation of **8**, 9-methyl-8-oxoadenine (**6**)[3] was benzylated with $PhCH_2Br$ in $AcNMe_2$ (100—102°C, 6 h) to give, after basification, the 1-benzyl derivative **7**·H_2O [mp 214—215°C (dec.)][6] in 76% yield (Scheme 1). On treatment with boiling 1 *N* aqueous NaOH for 1 h, **7**·H_2O underwent Dimroth rearrangement, producing the N^6-benzyl isomer **8** (mp 207.5—208.5°C) in 99% yield. This two-step conversion was analogous to that employed recently by us[3,4] for the synthesis of **3** from **6** through **2**. Treatment of **8** with MeI in $AcNMe_2$ (46°C, 79 h) furnished the 3-methylated product **9** [83% yield; mp 232—233°C (dec.)] together with the 1-methylated product **12**·H_2O [5%; mp 214.5—215°C (dec.)]. The 1-methyl structure of the latter product was evidenced by its conversion into the hydrochloride salt **13**·$2H_2O$ [88%; mp 217—218°C (dec.)] by use of Amberlite IRA-402 (Cl^-) and subsequent catalytic hydrogenolysis [20% $Pd(OH)_2$–C/H_2,[7] H_2O, 1 atm, room temp., 4 h] to afford the known 1,9-dimethylpurine **2**[3] (73%; mp > 300°C). Similar conversion of the major methylation product **9** into the hydrochloride salt **10**·$1/2H_2O$ [99%; mp 249—250°C (dec.)], followed by catalytic hydrogenation [20% $Pd(OH)_2$–C/H_2, 50% (v/v) aqueous AcOH, 1 atm, 65—70°C, 6 h], gave the monocyclic amidine salt **5** [62%; mp



Scheme 1

218.5—219.5°C (dec.)],[8] supporting the correctness of the 3-methyl structure assigned to **9**.

The observed high selectivity at the 3-position in methylation of **8** encouraged us to carry out a similar methylation of the N^6-methyl analogue **3**. On treatment with MeI in $AcNMe_2$ (50—52°C, 48 h), **3** gave the 3-methylated product **11** [50%; mp 266—267°C (dec.)][9] and the 1-methylated product **15** [13%; mp 262.5—263.5°C (dec.)][10] as well.

These structure assignments to both products were made by analogy with the above methylation of **8** and by comparison of their UV spectra with those of **9** and **12**·H_2O. Treatment of **11** with Amberlite IRA-402 (Cl^-) in H_2O produced the hydrochloride salt **1** [mp 278.5—279.5°C (dec.)] in 98% yield. The synthetic **1** was identical (by mixture melting point test and comparison of the UV, IR, ^1H NMR, and mass spectra and TLC mobility) with a natural sample of caissarone hydrochloride. A similar anion exchange in **15** provided the corresponding hydrochloride **16**·$2H_2O$ [mp 247.5—249.5°C (dec.)], a positional isomer of **1**, in quantitative yield.

On the other hand, methylation of **3** with MeI in the presence of anhydrous K_2CO_3 in $HCONMe_2$ (room temp., 3 h) furnished the 7-methylated product **14** (mp 222—223°C)[11] in 79% yield. On treatment with 10% ethanolic HCl, **14** gave the hydrochloride **14**·HCl [mp 269—270°C (dec.)], another positional isomer of **1**, in 95% yield.

In conclusion, the present results exemplify that the N(3) atom of N^6-alkyl-9-methyl-8-oxoadenines (type **3** or **8**) is the most favored site of methylation among the nitrogens in the neutral species. Since the starting material **3** is obtainable from 9-methyladenine via a four-step route in 57% overall yield,[3] the above two-step synthesis of **1** from **3** through **11** formally concludes a six-step synthesis of caissarone hydrochloride (**1**) from 9-methyladenine in 28% overall yield.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research (C) (No. 01571148) from the Ministry of Education, Science and Culture, Japan. We are also grateful to Dr. Raymond Zelnik (São Paulo) for a gift of natural caissarone hydrochloride.

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3. (a) T. Fujii, T. Saito, and S. Mori, *Heterocycles*, **27**, 1145 (1988); (b) *Idem*, *Chem. Pharm. Bull.*, **38**, 2146 (1990).
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6. Satisfactory analytical and/or spectroscopic data were obtained for all new compounds described.

7. For a recent use of Pearlman's catalyst for hydrogenolytic cleavage of N–benzyl bond, see K. Yoshida, S. Nakajima, T. Wakamatsu, Y. Ban, and M. Shibasaki, *Heterocycles*, **27**, 1167 (1988).

8. Selected spectral data for **5**: UV λ_{max} [95% (v/v) aqueous EtOH] 252 nm (ε 200), 258.5 (230), 264 (190), 297 (180); ^{1}H NMR (Me_2SO-d_6) δ: 2.65 [3H, s, N(1)-Me], 3.23 [1H, dd, J = 10 and 7.5 Hz, C(5)-H_B], 3.81 [1H, dd, J = 10 Hz each, C(5)-H_A], 4.54 (2H, d, J = 5.5 Hz, NHC$\underline{H}_2$Ph), 4.6 [1H, m, C(4)-H], 6.93 [1H, d, J = 3 Hz, N(3)-H], 7.37 (5H, s, Ph), 9.28 and 9.38 (1H each, br, $=NH_2^+$), 10.10 (1H, dull t, J = 5.5 Hz, N$\underline{H}$CH_2Ph). The δ values in this paper are expressed in ppm downfield from internal Me_4Si.

9. UV λ_{max} [95% (v/v) aqueous EtOH] 224 nm (ε 30800), 301 (16300); λ_{max} [H_2O (pH 1)] 226 (31800), 296 (21300); λ_{max} [H_2O (pH 7)] 226 (32600), 304 (16200); λ_{max} [H_2O (pH 13)] 226 (32300), 310 (16900).

10. UV λ_{max} [95% (v/v) aqueous EtOH] 223 nm (ε 36300), 296 (10800); λ_{max} [H_2O (pH 1)] 226 (40100), 273 (9600), 292 (9300); λ_{max} [H_2O (pH 7)] 225 (37900), 290 (11500); λ_{max} [H_2O (pH 13)] 224 (33500), 286 (13100).

11. IR ν_{max} (Nujol): 3380 cm^{-1} (NH), 1690 (C=O); ^{1}H NMR (Me_2SO-d_6) δ: 2.90 (3H, d, J = 5 Hz, NH$\underline{Me}$), 3.25 and 3.50 (3H each, s, NMe's), 6.59 (1H, br, N$\underline{H}$Me), 8.11 [1H, s, C(2)-H].

(Received in Japan 4 October 1990)