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SYNTHESIS OF PHIDOLOPIN, 7-(4-HYDROXY-3-NITROBENZYL)-1,3-DIMETHYLXANTHINE FROM THE BRYOZOAN PHIDOLOPORA PACIFICA

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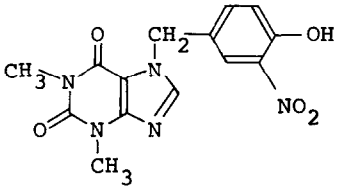
Summary: A total synthesis of a biologically active compound, phidolopin, was accomplished and its regioisomer was also synthesized.

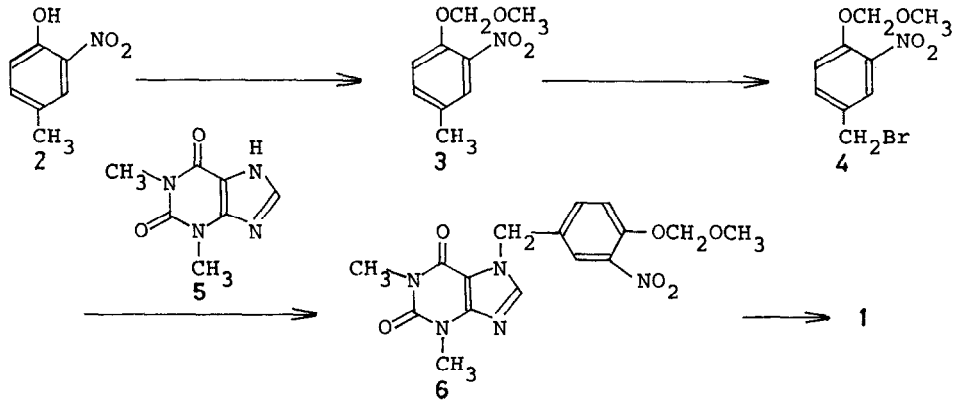
Phidolopin (**1**), a new xanthine derivative recently isolated from a marine organism, the bryozoan Phidolopora pacifica, shows antifungal and antialgal activities.[1] The structure of **1** has been determined by X-ray diffraction analysis,[1] but its total synthesis has not been achieved. Now we describe herein the synthesis of **1** and its analog (**8**) in a preparative scale.


Phidolopin (1)

2-Nitro-p-cresol (**2**) was employed as a starting material for the construction of the benzyl moiety of **1**. Thus, the cresol (**2**) was treated with CH_3OCH_2Cl in the presence of NaH in THF at room temperature to afford a protected cresol (**3**) as a pale yellow oil in 85% yield. Bromination of **3** with N-bromosuccinimide in CCl_4 using α,α'-azobis-iso-butyronitrile as a catalyst gave the benzyl bromide (**4**), mp 88-90°C.

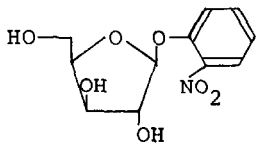
The reaction of theophylline (**5**) with **4** in the presence of K_2CO_3 in DMF at room temperature resulted in the smooth formation of methoxymethylphidolopin (**6**), mp 193-195°C, in 99% yield. [**6**: ^{1}H-NMR (400MHz, $CDCl_3$) δ: 3.40(3H, s), 3.51(3H, s), 3.59(3H, s), 5.28(2H, s), 5.48(2H, s), 7.33(1H, d, J=8.6Hz), 7.55(1H, dd, J=8.6, 2.2Hz), 7.65(1H, s), 7.78(1H, d, 2.2Hz); UV(EtOH) λ max 319 (ε 1160), 272(ε 8970)]. The substitution occurred regioselectively at the 7-position rather than at the 9-position.[2] This was easily judged on the basis of the characteristic UV spectrum of **6**.

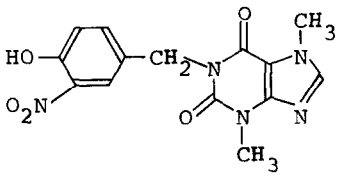
Finally, deprotection of **6** was accomplished under acidic conditions: heating of **6** with a catalytic amount of H_2SO_4 in acetic acid for 1h afforded phidolopin (**1**) in 79% yield. Its spectral and physical data are identical with those of natural phidolopin. The ^{13}C-NMR spectrum of **1** was also assigned.[3]



A previous work has demonstrated that a fungus, Rhizoctonia solani inhibited by phidolopin (1) produces a glycoside (7) containing an o-nitrophenol moiety.[4] The o-nitrophenol moiety seems to play a significant role for antifungal activity in the sight of the structure-activity relationships. Thus, we planed to synthesize the regioisomer of **1**, 1-(4-hydroxy-3-nitrobenzyl)-3,7-dimethylxanthine (8). Theobromine was similarly treated with the benzyl bromide (4) followed by the demethoxymethylation under acidic conditions. The expected compound (8), mp 254-256°C, was obtained in 91% yield.

The pharmacological evaluation of 1 and 8 are now in progress.





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References and Notes

1. S.W. Ayer, R.J. Andersen, H. Cun-heng, and J. Clardy, J. Org. Chem., 1984, **49**, 3869.
2. J.H. Lister "Fused Pyrimidines Part II Purines," in the series of The Chemistry of Heterocyclic Compounds, Wiley-Interscience, New York, 1971, p 223.
3. ^{13}C-NMR (100MHz, $CDCl_3$) δ : 28.0(q, CH_3), 29.7(q, CH_3), 49.0(t, $C_{1'}$),106.8(s, C_5), 121.0(d, $C_{6'}$ or $C_{3'}$), 124.5(d, $C_{3'}$ or $C_{6'}$), 128.1(s, $C_{2'}$), 133.7(s, $C_{4'}$), 137.0(d, $C_{7'}$), 140.6(d, C_8), 149.3(s, C_4), 151.6(s, C_6), 155.2(s, $C_{5'}$), 155.3(s, C_2).
4. W.B. Turner "Fungal Metabolites I," Academic press, London, 1971, p 305.

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