THE NOVEL RING OPENING OF AN OXAZOLO[5,4-d]PYRIMIDINE AND SUBSEQUENT REARRANGEMENT TO FORM AN IMIDAZO[4,5-d]PYRIMIDINE

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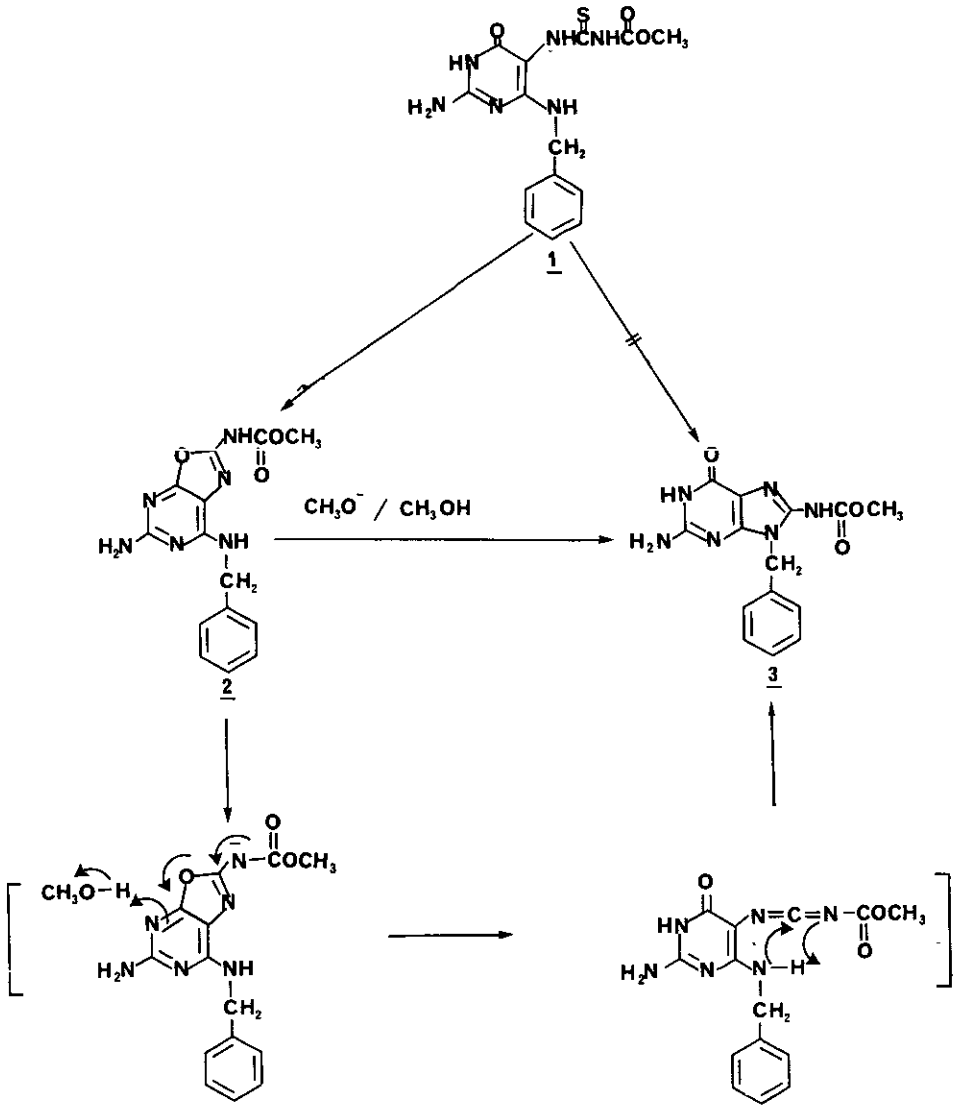
Abstract - A novel rearrangement from methyl 6-amino-4-benzylaminooxazolo-[5,4-d]pyrimidine-2-carbamate to methyl 9-benzylguanine-8-carbamate (3) is described.

Our attempt to synthesize methyl 9-benzylguanine-8-carbamate (3) by a direct cyclodesulfurization of 2-amino-4-benzylamino-5-[1-(3-methoxycarbonyl)thioureido]pyrimidin-6-one (1) with dicyclohexylcarbodiimide was unsuccessful. Using the reaction conditions which were specifically designed to effect a direct conversion of 1 to 3, we have obtained only 6-amino-4-benzylaminooxazolo[5,4-d]pyrimidine-2-carbamate (2). However, we have now developed reaction conditions which effect a novel ring opening of compound 2 followed by a rearrangement and recyclization to afford compound 3. In essence, this represents a facile conversion of compound 1 into compound 3. It has been well documented that various 1,2,4-oxadiazoles undergo a mononuclear heterocyclic rearrangement to various heterocyclic compounds under experimental conditions such as heating or treatment with a base, i.e., potassium hydroxide or sodium methoxide in methanol[2,3]. Also numerous 7-aminooxazolo[5,4-d]pyrimidines are known to undergo an intramolecular rearrangement to imidazo[4,5-d]pyrimidin-6-ones by heating in formamide or dilute sodium hydroxide[4,5]. The mechanism postulated for the rearrangement of these oxazolo[5,4-d]pyrimidines to an imidazo[4,5-d]pyrimidine assumes that an initial nucleophilic substitution occurs at the carbon atom of the oxazole ring effecting a ring opening to an intermediate 5-acylamino-4-amino-6-oxopyrimidine anion. Subsequent annulation through nucleophilic attack of the C-4 amino group on the acyl carbonyl carbon then affords the imidazo[4,5-d]pyrimidine ring system. To the best of our knowledge, an intramolecular ring-opening-recyclization of a 7-aminooxazolo[5,4-d]pyrimidine which proceeds through a carbodiimide intermediate to an imidazo- [4,5-d]pyrimidine has not been described. We now wish to report a facile synthetic procedure for the synthesis of compound 3 from compound 2 through a presumed carbodiimide intermediate.

A mixture of compound 2[1] (2.45 g, 7.8 mmoles), anhydrous potassium carbonate (2.2 g, 15.6 mmoles) in anhydrous methanol (50 mL) was heated under reflux for 5 hours. The solvent was

removed in vacuo and the resulting solid was dissolved in water (20 mL). Upon the addition of an aqueous ammonium chloride solution [1.68 g, (31.2 mmoles) in water (20 mL)] the solid which had precipitated was collected by filtration. The solid was washed with cold water (10 mL) and then



methanol (5 mL) to furnish 2.13 g (87%) of crude compound 3. The solid was recrystallized from a DMF and methanol mixture (1:1); mp 321-322° dec.; ir (KBr): 3450, 3280, 2920, 1740 cm^{-1};

^{1}H NMR (DMSO-d_6): δ 3.4 (s, 3 H, CH_3), 5.1 (s, 2 H, CH_2), 6.58 (s, 2 H, NH_2, D_2O exchangeable), 7.3 (m, 5 H, Ar-H), 9.8 (br, 1 H, NH, D_2O exchangeable), 10.7 (s, 1 H, NH, D_2O exchangeable); uv: $\lambda_{max}^{pH\ 7}$ 266 nm (ε 1.7 x 10^4), $\lambda_{max}^{pH\ 1}$ 259 nm (ε 1.8 x 10^4), $\lambda_{max}^{pH\ 11}$ 264 nm (ε 1.4 x 10^4), 273 nm (ε 1.3 x 10^4), 289 nm (ε 1.4 x 10^4). A reasonable mechanism for this reaction involves the initial abstraction of a proton from the 2-carbamoyl moiety of compound 2, followed by an opening of the oxazole ring to give a carbodiimide intermediate. Subsequent addition of the C-4-amino nucleophile to the carbon atom of the carbodiimide, then furnishes the imidazo[5,4-d]pyrimidin-6-one derivative 3.

The mechanism of this facile rearrangement and its application to the synthesis of other heterocyclic systems is under further investigation in our laboratory.

ACKNOWLEDGEMENTS

This investigation was supported by the UNDP/World Bank/WHO Special Program for Research and Training in Tropical Diseases and the Scientific Working group of filariasis (I.D. 800134). Ji-Wang Chern was the recipient of a fellowship from The National Science Council of The Republic of China. The authors would like to thank Ms Deanna VanSickle for her assistance in the preparation of this manuscript.

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Received, 25th May, 1984