SYNTHESIS OF 5-[1-(3-METHYLCARBONYL)-O-METHYLPSEUDOURIDE]URACIL: A NOVEL
METHOD FOR THE CONVERSION OF AN \(H\,H'-\)DISUBSTITUTED THIOUREA INTO AN
O-METHYL-\(H\,H'-\)DISUBSTITUTED PSEUDOUREA

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Abstract - Treatment of 5-[1-(3-methoxycarbonyl)thioureido]uracil with
dicyclohexylcarbodiimide in methanol has resulted in the formation of
5-[1-(3-methoxycarbonyl)-O-methylpseudouride]uracil.

A literature survey has revealed that several methods are available for the preparation of
O-alkylpseudoureas from carboximidates.\(^1\,^2\) In the absence of catalysis, however, the reaction
of carboximidates with alcohols proceeds poorly and only under very drastic conditions, i.e.,
pressure and/or at high temperature.\(^3\) It has been reported\(^4\) that alcohols in the presence of
sodium alkoxide, react exothermally with carboximidates to afford the corresponding O-alkyl
pseudoureas in near quantitative yields. Synthesis of O-alkyl pseudoureas using carboximide
also has been accomplished with copper or zinc salts as catalysts.\(^5\,\,^6\) However, to the best of
our knowledge, the facile addition of alcohols to carboximidates without the use of a catalyst or
the aid of a sodium alkoxide, which should be of value with base sensitive compounds, has not yet
been reported.

The equilibrium established between a reaction of dicyclohexylcarbodiimide (DCC) and a thiourea
derivative\(^7\), with the subsequent ring cyclization reaction of these ortho-substituted thiourea
adducts to afford the various heterocyclic systems\(^8\), has been studied. Recently, we reported
on the use of DCC to accomplish the cyclodesulfurization of a 2.4-diamino-5-[1-(3-methoxycar-
bonyl)thioureido]pyrimidin-6-one in dimethylformamide (DMF) to furnish the oxazolo[5,4-d]-
pyrimidine ring system\(^9\). To explore the scope of this synthetic methodology, we elected to
synthesize methyl oxazolo[5,4-d]pyrimidin-6-one-2-carbamate (2) by reacting 5-[1-(3-methoxy-
carbonyl)thioureido]uracil (1)\(^10\) with DCC in DMF at room temperature. However, due to the
insolubility of 1 in DMF, the reaction was not successful.

A subsequent reaction of compound 1 with DCC was performed in methanol at reflux temperature
to obtain a good yield of a single product which initially appeared to be the desired product 2.
This product gave \(^1\)H NMR, \(^13\)C NMR, UV spectral data and elemental analysis as follows: \(^1\)H
NMR (DMSO-\(d_6\)): \(\delta\) 3.6 (s, 3 H, CH\(_3\)), 3.8 (s, 3 H, CH\(_3\)), 7.58 (s, 1 H, \(=\text{C}-\text{H}\)), 10.2 (s, 1 H,
NH, D\(_2\)O exchangeable). 11.28 (br, 2 H, D\(_2\)O exchangeable): \(^13\)C NMR (DMSO-\(d_6\)): \(\delta\)
149.9 (C-2), 160.6 (C-4), 111.3 (C-5), 131.9 (C-6), 163.0 (C=O), 160.8 (C=O), 52.3 (COOCH\(_3\)),
55.1 (O-CH₃); UV (pH) λₘₐₓ nm (ε x 10⁴): (pH 7) 288 (1.1); (pH 1) 261 (0.85); (pH 11) 291 (1.0); Anal. Calcd. for C₆H₇N₄O₅ (242.19): C, 39.67; H, 4.16; N, 23.13; Found: C, 39.90; H, 4.21; N, 23.37; and while it was obvious that these data did not support structure 2, they did seem to be compatible with a simple methanol adduct of the desired compound 2.

This seemed like a reasonable assumption since there have been many reports that Michael additions occur quite often as an intermediate step in a variety of phenomena involving pyrimidines. If a Michael addition had occurred at C-6 of compound 1, the resulting compound would be expected to possess characteristics similar to those previously reported for the addition of methanol to the 5,6-double bond of 5-diazouracil. In the ¹H NMR spectra, this 5-diazouracil methanol adduct has demonstrated an upfield chemical shift (δ 5.72) for the C-6 proton. However, the ¹H NMR spectrum of our compound revealed that a downfield chemical shift
(Δ 7.58) had occurred for the C-6 proton. This suggested that the C-6 proton of the uracil moiety in our target compound was still incorporated in a conjugated aromatic (uracil) electronic system. The $^{13}$C NMR chemical shift observed for the uracil ring carbons of our final product remained unchanged from the shifts observed for the ring carbons of 1 and are in agreement with values previously reported. Also, the mass spectrum showed an ion at $M^+ - 32$ which is characteristic for the loss of methanol, and the ions at $m/z$ 69 and 110 can be attributed to subsequent fragmentation of the $M^+ - 32$ fragment. On the basis of these data, vide infra, we have assigned the structure of our product as 5-[(3-methoxycarbonyl)-O-methylpseudoureido]-uracil (2).

We have now reported the first addition of an alcohol to a carbodiimide intermediate which had been generated in situ from an adduct prepared by the reaction of a thiourea derivative with DCC. This synthetic method is currently being applied to the synthesis of various 5-substituted uracils and their corresponding nucleosides in our laboratory.

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10. 5-[(3-Methoxycarbonyl)thioureido]uracil (1) was prepared in 94% yield by a condensation of 5-aminouracil (0.44 g, 3.5 mmoles) with methoxycarbonyl isothiocyanate\textsuperscript{11} (methoxycarbonyl isothiocyanate was prepared by adding methyl chloroformate (0.53 mL, 6.9 mmole) to a suspension of potassium thiocyanate (0.67 g, 6.9 mmole) in acetonitrile (15 mL) with stirring at 70°C for 30 min) in acetonitrile at reflux temperature for 2 hours. \textsuperscript{1}H NMR (DMSO-d\textsubscript{6}): δ 3.4 (s, 3 H, CH\textsubscript{3}), 8.9 (d, 1 H, J = 6 Hz, = C-H) 10.9 (d, 1 H, J = 6 Hz, NH, D\textsubscript{2}O exchangeable), 11.4 (s, 1 H, NH, D\textsubscript{2}O exchangeable), 11.65 (s, 1 H, NH, D\textsubscript{2}O exchangeable), 11.75 (s, 1 H, NH, D\textsubscript{2}O exchangeable). \textsuperscript{13}C NMR (DMSO-d\textsubscript{6}): δ 149.4 (C-2), 160.7 (C-4) 113.7 (C-5), 131.1 (C-6), 176.1 (C=S), 153.9 (C=O), 53.0 (OCH\textsubscript{3}). UV (pH) \(\lambda_{\text{max}}\) nm (\(\epsilon \times 10^4\)): (pH 7) 259 (2.2): 311 (1.0): (pH 10) 259 (2.0): (pH 11) 260 (1.6). IR (KBr): 1780 (C=O) cm\textsuperscript{-1}. Anal. Calcd. for C\textsubscript{7}H\textsubscript{8}N\textsubscript{4}O\textsubscript{4} (244.22): C, 34.43; H, 3.30; N, 22.94. Found: C, 34.54; H, 3.36; N, 23.11.


15. The exocyclic pseudourea moiety of compound 3 may exist in two tautomeric forms
\[-\text{NHC(OCH}_3\text{)}=\text{NCO}_2\text{CH}_3\text{ and/or } -\text{N}\text{=C(OCH}_3\text{)}\text{NCO}_2\text{CH}_3\].

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