# Use of $Eu(fod)_3$ Shift Reagent and Solvent Effects in Structural Elucidation of Novel Isomeric Pyrimidones and Model Methoxylated Pyrimidines[1]

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1-Ethyl-1,6-dihydro-2,4-dimethoxy-5-methyl-6-oxopyrimidine (**1***a*) and 1,5-diethyl-1,6-dihydro-2,4-dimethoxy-6-oxopyrimidine (**2***a*) are shown to be the correct positional isomers, respectively, for the major *O,O*-dimethyl derivatives isolated from the reaction products of 1-ethyl-5-methylbarbituric acid (**1**) and the new 1,5-diethylbarbituric acid (**2**) with excess diazomethane. In addition to the above compounds, the behavior of 2,4-dimethoxypyrimidine (**3**), 4,6-dimethoxypyrimidine (**4**), 2,4,6-trimethoxypyrimidine (**5**), and 6-chloro-2,4-dimethoxypyrimidine (**6**) were studied by p.m.r. spectrometry in various solvents. The relatively new shift reagent, $Eu(fod)_3$ was used in these studies because of its affinity for weak electron donors such as ethers.

On montre que le 1-éthyl-1,6-dihydro-2,4-diméthoxy-5-méthyl-6-oxopyrimidine (**1***a*) et le 1,5-diéthyl-1,6-dihydro-2,4-diméthoxy-6-oxo-pyrimidine (**2***a*) sont les isomères de position corrects, respectivement pour les dérivés principaux *O,O*-diméthyl isolés des produits de réaction de l'acide 1-éthyl-5-méthylbarbiturique (**1**) et du nouvel acide 1,5-diéthylbarbiturique (**2**) avec le diazométhane. En plus des composés précédents, le comportement du 2,4-diméthoxypyrimidine (**3**), du 4,6-diméthoxypyrimidine (**4**), du 2,4,6-triméthoxypyrimidine (**5**), et du 6-chloro-2,4-diméthoxypyrimidine (**6**) a été étudié par spectrométrie r.m.p. dans différents solvants. On a utilisé le relativement nouvel agent de déplacement $Eu(fod)_3$ dans ces études à cause de son affinité pour les donneurs faibles d'électrons tels que les éthers.

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## Introduction

In an earlier paper (1), where it was shown that *N*-methylation of 5,5-disubstituted barbiturates is predominant with the methylating agent diazomethane, reference was made to the formation of various products with *O*-methyl proton signals from 1,5-dialkylbarbituric acids by the action of excess diazomethane. Although no difficulty was experienced in recognizing the nature of the substituents of these products by p.m.r. spectrometry, the correct positional isomerism could not be established from the usual p.m.r., i.r., and mass spectral data. In addition, the various isomers are not easily and unambiguously obtained by alternative synthesis. It is the purpose of this communication to establish that **1***a* and **2***a* are the correct structures for the crystalline *O,O*-dimethyl derivatives isolated from 1-ethyl-5-methylbarbituric acid (**1**) and 1,5-diethylbarbituric acid (**2**), respectively, by the action of diazomethane. In arriving at these structural assignments, use has been made of the recently reported tris-1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione)-europium(III), $Eu(fod)_3$, as a paramagnetic shift reagent (2) and of solvent effects in p.m.r. spectrometry. The $Eu(fod)_3$ shift reagent appears to be superior to the more common and somewhat older shift reagent, tris-(dipivalomethanato)europium, $Eu(DPM)_3$, recently reviewed by Sanders and Williams (3), because it is more soluble than $Eu(DPM)_3$ in non-alcoholic solvents and has complexing properties such that it will affect weak electron donors such as ethers and esters. For comparison, four model pyrimidines of known structure, 2,4-dimethoxypyrimidine (**3**), 4,6-dimethoxypyrimidine (**4**), 2,4,6-trimethoxypyrimidine (**5**), and 6-chloro-2,4-dimethoxypyrimidine (**6**), were subjected to similar solvent and shift reagent studies. An earlier example of the application of these techniques for structural elucidation of isomeric pyrimidone and uracil derivatives has been reported from these laboratories (4).

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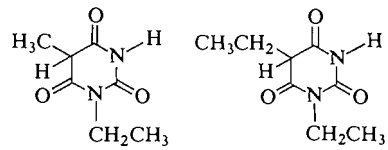
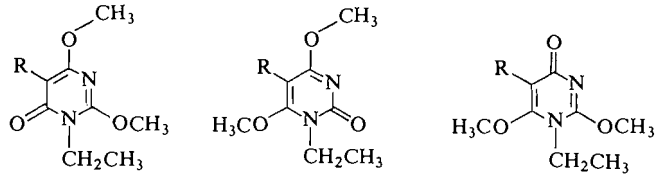
## Results and Discussion

### *Structural Elucidation of the Pyrimidones*

Excluding *O,N*-dimethyl derivatives which are minor products of the action of excess diazomethane in 1-ethyl-5-methylbarbituric acid (**1**) and 1,5-diethylbarbituric acid (**2**), only one of the structures **1***a*, *b*, *c* and **2***a*, *b*, *c*, respectively



**1** **2**



**1***a* R = $CH_3$ **1***b* R = $CH_3$ **1***c* R = $CH_3$
**2***a* R = $CH_2CH_3$ **2***b* R = $CH_2CH_3$ **2***c* R = $CH_2CH_3$

TABLE 1. The p.m.r. solvent shift data ($\delta$ in p.p.m. downfield from internal TMS)
1-Ethyl-1,6-dihydro-2,4-dimethoxy-5-methyl-6-oxopyrimidine (**1***a*)

| Solvent | O—Me (C-2) | O—Me (C-4) | $CH_2$(Et) (N-1) | $CH_3$ (C-5) | $CH_3$(Et) (N-1) |
|---|---|---|---|---|---|
| $CCl_4$ | 3.97 (s) | 3.85 (s) | 3.93 (q) | 1.77 (s) | 1.18 (t) |
| $\Delta^{CCl_4}_{C_6H_6}$ | +0.40 | +0.48 | +0.08 | −0.43 | +0.13 |
| $\Delta^{CCl_4}_{C_5H_5N}$ | +0.15 | +0.05 | −0.05 | −0.32 | +0.03 |
| $\Delta^{CCl_4}_{TFA}$ | −0.37 | −0.38 | −0.47 | −0.40 | −0.25 |

1,5-Diethyl-1,6-dihydro-2,4-dimethoxy-6-oxopyrimidine (**2***a*)

| Solvent | O—Me (C-2) | O—Me (C-4) | $CH_2$(Et) (N-1) | $CH_2$(Et) (C-5) | $CH_3$(Et) (N-1) | $CH_3$(Et) (C-5) |
|---|---|---|---|---|---|---|
| $CCl_4$ | 3.98 (s) | 3.85 (s) | 3.92 (q) | 2.30 (q) | 1.18 (t) | 0.97 (t) |
| $\Delta^{CCl_4}_{C_6H_6}$ | +0.40 | +0.47 | +0.08 | −0.47 | −0.12 | −0.08 |
| $\Delta^{CCl_4}_{C_5H_5N}$ | +0.17* | +0.03* | −0.07 | −0.37 | −0.02 | −0.17 |
| $\Delta^{CCl_4}_{TFA}$ | −0.37 | −0.40 | −0.48 | −0.38 | −0.27 | −0.20 |

*In pyridine, these peaks resolved by 0.01 p.p.m. (s) singlet, (q) quartet, (t) triplet.

can be assigned to the major *O,O*-dimethyl product from each of **1** and **2**.

Using the solvent shift data of Table 1, one can deduce the most likely structure for the positional *O,O*-dimethyl isomer formed from each of **1** and **2**. For ketones and ethers, the magnitude and sign of the proton resonance solvent shifts have been rationalized by means of reference plane rules (5–7). These rules have been generalized (8, 9): protons lying in front of the plane will tend to be deshielded in benzene (relative to an "inert" solvent) while those behind the plane will tend to be shielded in benzene. The shifts ($\Delta = \delta CCl_4 - \delta C_5H_5N$ p.p.m.) observed for pyridine are in general more negative than the corresponding benzene-induced shifts (10). The carbonyl plane "rule" is also applicable to pyridine-induced solvent shifts in some ketones (11), but the reference plane is displaced so that it passes through the α-carbons rather than the carbonyl carbon (10). By these rules one finds that the benzene shifts ($\Delta = \delta CCl_4 - \delta C_6H_6$ p.p.m.) support structures **1***a* and **2***a* best, and similarly, the pyridine shifts support structures **1***a* and **2***a* best.

Some use has been made of the solvent shifts for methoxy-group resonances induced by trifluoroacetic acid (TFA) (12, 13) as an aid to structural elucidation. The downfield shift by

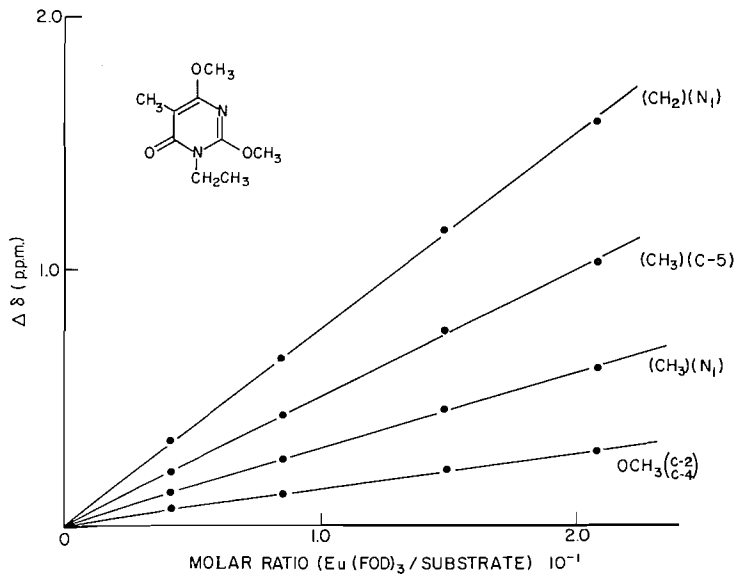



FIG. 1. Normalized Eu(fod)$_3$ induced p.m.r. shifts for 1-ethyl-1,6-dihydro-2,4-dimethoxy-5-methyl-6-oxopyrimidine (**1***a*) in $CDCl_3$ solution.

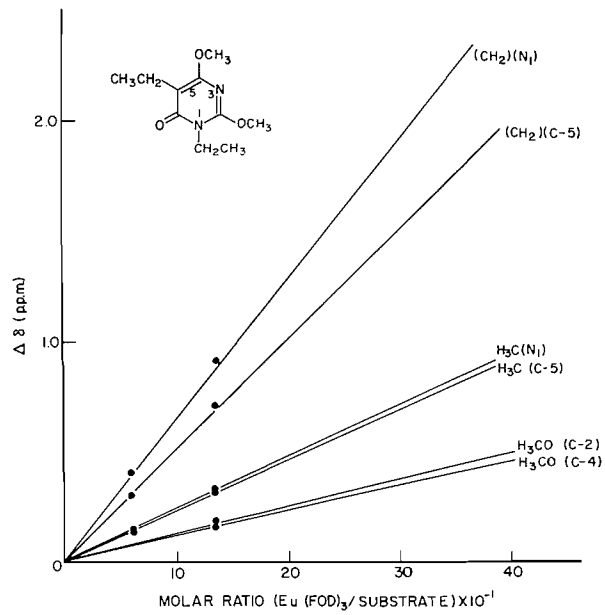



FIG. 2. Normalized Eu(fod)$_3$ induced p.m.r. shifts for 1,5-diethyl-1,6-dihydro-2,4-dimethoxy-6-oxopyrimidine (**2***a*) in $CDCl_3$ solution.

TFA ($\Delta = \delta CCl_4 - \delta TFA$ p.p.m.) for methoxy-group resonances of several methoxybenzenes has been attributed to protonation of the methoxy group (12) whereas with flavones protonation by TFA at both methoxy and carbonyl groups has been proposed (13). The TFA solvent shift data of Table 1 support structures **1***a* and **2***a* best assuming protonation at the carbonyl oxygen only.

The structural assignments for **1***a* and **2***a*, based on solvent studies, were confirmed from chemical shift behavior (Figs. 1 and 2) observed

TABLE 2. Variation of deshielding gradients with functionality

| Compound | Functional group | Gradient (p.p.m./mol $Eu(fod)_3$ per mol substrate) | Solvent |
|---|---|---|---|
| **1***a* | $CH_2$ (N-1) | 7.5 | $CDCl_3$ |
| | $CH_3$ (C-5) | 4.9 | |
| | $CH_3$ (N-1) | 3.0 | |
| | $OCH_3$ (C-2,3) | 1.4 | |
| **2***a* | $CH_2$ (N-1) | 6.3 | $CDCl_3$ |
| | $CH_2$ (C-5) | 5.1 | |
| | $CH_3$ (N-1) | 2.3 | |
| | $CH_3$ (C-5) | 2.3 | |
| | $OCH_3$ (C-2) | 1.2 | |
| | $OCH_3$ (C-4) | 1.1 | |
| **3** | $OCH_3$ (C-2) | 7.8 | $CDCl_3$ |
| | $OCH_3$ (C-4) | 4.4 | |
| | H (C-5) | 3.7 | |
| | H (C-6) | 1.5 | |
| **4** | H (C-5) | 5.7 | $CDCl_3$ |
| | $OCH_3$ (C-2,4,6) | 4.3 | |
| **5** | H (C-5) | 6.0 | $CCl_4$ |
| | $OCH_3$ (C-4,6) | 4.8 | |
| | $OCH_3$ (C-2) | 4.5 | |
| **6** | $OCH_3$ (C-2) | 6.3 | $CDCl_3$ |
| | $OCH_3$ (C-4) | 3.9 | |
| | H (C-5) | 3.7 | |

with $Eu(fod)_3$, shift reagent. In selecting **1***a* as the correct structure, it was noted that both methoxy resonances are nearly equally affected by the shift reagent and have the same deshielding gradients of 1.4 p.p.m. (Table 2). Although structure **1***b* is best suited by symmetry for this deshielding, assuming complexation at the carbonyl oxygen by the shift reagent, the asymmetrical location of one ring nitrogen would not be expected to alter the chemical shifts greatly. In contrast, the similarly strong deshielding of both the $CH_2$(Et) protons at N-1 and of the C-5 methyl protons (gradients of 7.5 and 4.9 p.p.m., respectively) by the shift reagent can only be accounted for on the basis of structure **1***a*. Confirmation of structure **2***a* was likewise based on the similarity of deshielding of the methoxy resonances (gradients of 1.1 and 1.2 p.p.m., Table 2) and on the similar but larger deshielding of the $CH_2$(Et) and $CH_3$(Et) protons at N-1 and C-5 (gradients of 6.3, 2.3 and 5.1, 2.3 p.p.m., respectively). It is concluded, therefore, that the major products formed by the action of diazomethane on **1** and **2** are 1-ethyl-1,6-dihydro-2,4-dimethoxy-5-methyl-6-oxopyrimidine (**1***a*) and 1,5-diethyl-1,6-dihydro-2,4-dimethoxy-6-oxopyrimidine (**2***a*), respectively.

*Solvent and $Eu(fod)_3$ Shift Studies with Some Methoxylated Pyrimidines*

The assignment of chemical shifts to methoxylated and methylated pyrimidine rings has been difficult due to very small or negligible differences in these values among structurally similar derivatives. Nishiwaki (14) has reported that the methoxy signal of 2,4-dimethoxy-6-methylpyrimidine appears as a singlet in carbon tetrachloride (3.83 p.p.m.) or in acetic acid (4.00 p.p.m.) while two distinct bands (4.33 and 4.27 p.p.m.) were seen for this pyrimidine in trifluoroacetic acid. The signal at lower field was assumed to be the C-2 methoxy because this signal is likely to be affected more extensively by protonation of the nitrogen atom. Ma and Warnhoff (15) have reported that methoxyl groups show a negligible shift (+0.03 to −0.11 p.p.m.) on changing from deuterochloroform to perdeuteroacetic acid and only a small (−0.08 to −0.37 p.p.m.) further downfield shift in trifluoroacetic acid.

In considering the assignment of the correct structure *a*, *b*, or *c* to compounds **1** and **2**, the known compounds 2,4-dimethoxypyrimidine (**3**), 4,6-dimethoxypyrimidine (**4**), 2,4,6-trimethoxypyrimidine (**5**), and 6-chloro-2,4-dimethoxypyrimidine (**6**) were studied for solvent effects in the hope that frequency assignments made with this series of compounds would aid in the structural elucidation of **1** and **2**. These frequency data (Table 3), however, do not prove helpful by analogy in selecting the correct structure for **1** and **2**. The aromatic solvent shifts indicate that competitive complexation is occurring at different sites with the simpler substrates (**3**–**6**) to produce the range of values observed. Competitive complexation undoubtedly contributes to the character of the solvent shifts recorded for **1** and **2** even though these two compounds possess a carbonyl function which usually exerts a stronger polarizing influence in such solvent effects.

The relative solvent shifts for **3**, **4**, **5**, and **6** in trifluoroacetic acid ($\Delta_{TFA}^{CCl_4}$) (Table 3) show the largest downfield shift for the C-5 proton with

TABLE 3. The p.m.r. solvent shift data ($\delta$ in p.p.m. downfield from internal TMS) for some methoxylated pyrimidines

| Solvent | C-5 | C-6 | OMe C-2 | OMe C-4 | OMe C-6 | H(C-2) | $J^*H_5,H_6$(Hz) |
|---|---|---|---|---|---|---|---|
| 2,4-Dimethoxypyrimidine (**3**) | | | | | | | |
| $CDCl_3$ | 6.37(d)† | 8.18(d) | 4.00 | 3.97 | — | | 5.6 |
| $CCl_4$ | 6.27(d) | 8.10(d) | 3.92 | 3.92 | — | | 5.8 |
| $\Delta^{CCl_4}_{C_6H_6}$ | +0.24 | +0.22 | +0.17 | +0.32 | | | 5.8 ($C_6H_6$) |
| $\Delta^{CCl_4}_{C_5H_5N}$ | −0.11 | −0.13 | 0.00 | +0.09 | | | 5.7 ($C_5H_5N$) |
| $\Delta^{CCl_4}_{TFA}$ | −0.56 | −0.12 | −0.46 | −0.41 | | | 7.0 (TFA) |
| 4,6-Dimethoxypyrimidine (**4**) | | | | | | | $J^*H_2,H_5$(Hz) |
| $CDCl_3$ | 6.03(d) | — | — | 3.95 | 3.95 | 8.45 (d) | 0.8 |
| $CCl_4$ | 5.93(d) | — | — | 3.90‡ | 3.90‡ | 8.33 (d) | 0.7 |
| $\Delta^{CCl_4}_{C_6H_6}$ | −0.12 | — | — | +0.23 | +0.23 | −0.15 | 0.8 ($C_6H_6$) |
| $\Delta^{CCl_4}_{C_5H_5N}$ | −0.24 | — | — | +0.02 | +0.02 | — | 0.9 ($C_5H_5N$) |
| $\Delta^{CCl_4}_{TFA}$ | −0.69 | — | — | −0.38 | −0.38 | −0.45 | 0.6 (TFA) |
| 2,4,6-Trimethoxypyrimidine (**5**) | | | | | | | |
| $CDCl_3$ | 5.72 | — | 3.98 | 3.93 | 3.93 | | |
| $CCl_4$ | 5.58 | — | 3.90 | 3.88 | 3.88 | | |
| $\Delta^{CCl_4}_{C_6H_6}$ | −0.22 | — | +0.22 | +0.25 | +0.25 | | |
| $\Delta^{CCl_4}_{C_5H_5N}$ | −0.29 | — | 0.00 | +0.03 | +0.03 | | |
| $\Delta^{CCl_4}_{TFA}$ | −0.57 | — | −0.42 | −0.34 | −0.34 | | |
| 6-Chloro-2,4-dimethoxypyrimidine (**6**) | | | | | | | |
| $CDCl_3$ | 6.40 | — | 4.02 | 3.97 | — | | |
| $CCl_4$ | 6.32 | — | 3.95‡ | 3.95‡ | — | | |
| $\Delta^{CCl_4}_{C_6H_6}$ | +0.17 | — | +0.33 | +0.45 | — | | |
| $\Delta^{CCl_4}_{TFA}$ | −0.60 | — | −0.47 | −0.42 | — | | |

*Measured on the 100 Hz sweep width.
†d, Doublet.
‡No resolution on the 100 Hz sweep width.

smaller deshielding for the C-2 proton (*e.g.* **4**) or for the methoxyl protons at C-2 (*e.g.* **3**, **5**, **6**). These shifts are in accord with some delocalization of charge through a protonated nitrogen atom; however, the larger downfield shift for the C-5 proton is opposite to what Nishiwaki found for TFA solutions of 4-hydroxy-6-methylpyrimidine and 5-bromo-4-hydroxy-6-methylpyrimidine (14) where the C-2 proton moves downfield more than 1 p.p.m. in TFA relative to chloroform. Similarly, the results of these studies of the effect of TFA on the simpler substrates (**3**–**6**) are of little help in selecting the correct structures for **1** and **2** where protonation of the carbonyl oxygen appears to be more favored than a ring nitrogen.

In studying the effect of Eu(fod)$_3$ on 2,4-dimethoxypyrimidine (**3**), one is surprised to find that it is the C-2 methoxy protons which show the largest deshielding gradient (7.8 p.p.m.) Table 2 and Fig. 3. It would appear that complexation[2] of Eu(fod)$_3$ involves the C-2 methoxy oxygen rather than the C-4 methoxy oxygen atom which might have been expected to have the higher electron density. Reversal of the methoxy assignments shows appreciable non-linearity in graphical representation of the C-4 methoxy proton shifts. It is also interesting to note from Fig. 3 that the deshielding gradient (3.7 p.p.m.) for the C-5 proton of 2,4-di-

[2]A referee has noted that complexation may involve a nitrogen of the pyrimidine ring instead of the oxygen of an *O*-methyl group because of the fact that pyridine is tightly complexed with lanthanide reagents while anisole is not. While this may be the case for some pyrimidine derivatives, complexation does not appear to involve the N-1 site, more favored than N-3 as a Lewis base, of 2,4-dimethoxypyrimidine because H (C-6) shows the smallest deshielding gradient (Fig. 3) of all protons of this molecule.

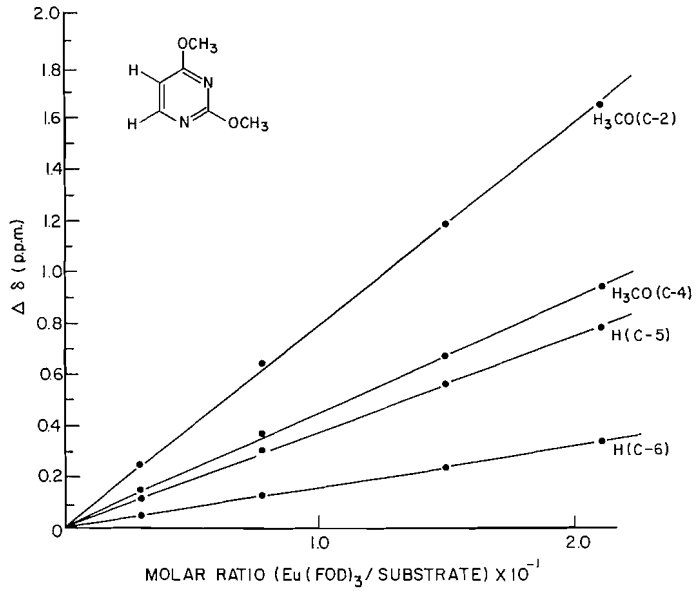



FIG. 3. Normalized $Eu(fod)_3$ induced p.m.r. shifts for 2,4-dimethoxypyrimidine in $CDCl_3$ solution.

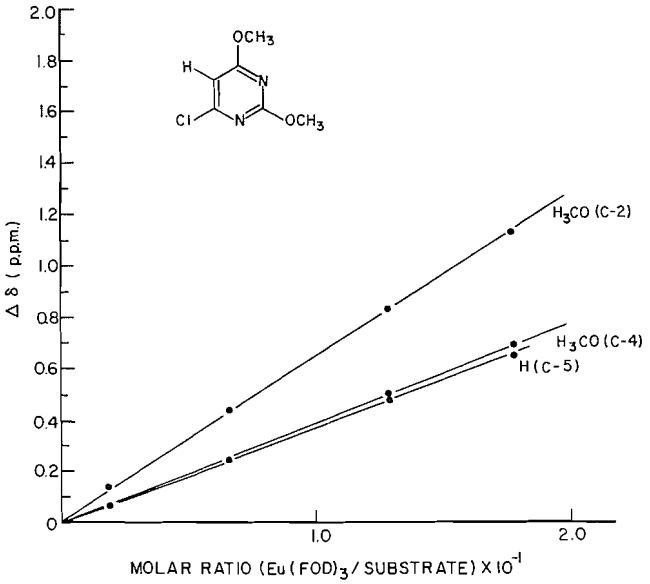



FIG. 4. Normalized $Eu(fod)_3$ induced p.m.r. shifts for 6-chloro-2,4-dimethoxypyrimidine in $CDCl_3$ solution.

methoxypyrimidine is significantly greater than that for the C-6 proton which is more proximate to the site of complexation. This reversal in deshielding effect with distance may be due to a dominant ring inductive effect influencing the para-proton more than the meta-proton, or it may arise in this instance by the influence of the angular dependence term ($3 \cos^2 X_i - 1$) of the McConnell equation (16) applicable to pseudo-contact complexation. Recent mathematical considerations of the geometry in regions of angular dependence for simple model compounds showing an anomalous upfield shift with Eu shift reagents have shown that the

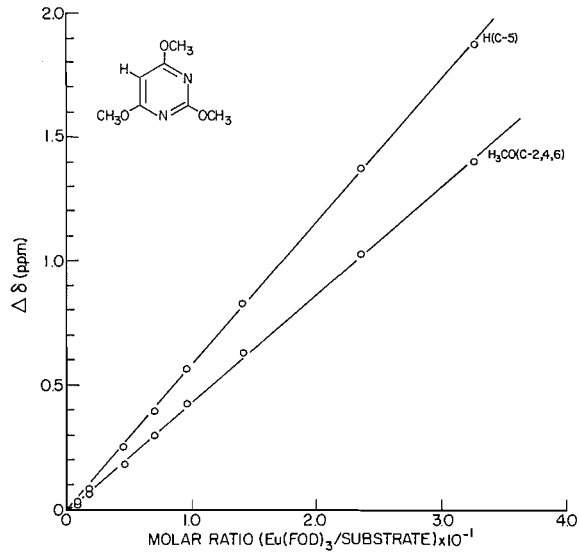



FIG. 5. Normalized Eu(fod)$_3$ induced p.m.r. shifts for 2,4,6-trimethoxypyrimidine in $CDCl_3$ solution.

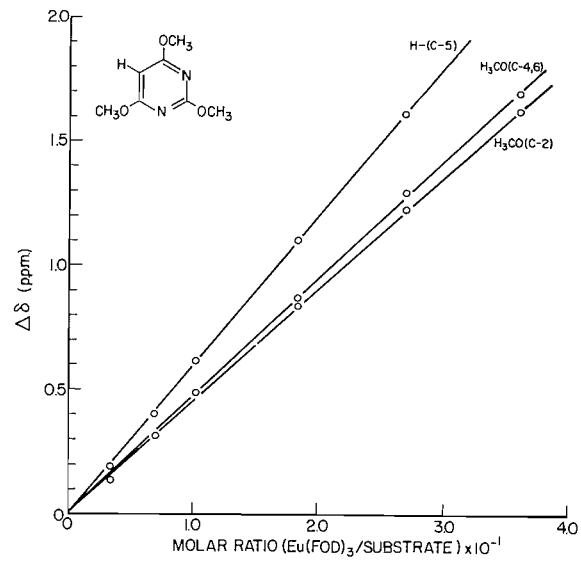



FIG. 6. Normalized Eu(fod)$_3$ induced p.m.r. shifts for 2,4,6-trimethoxypyrimidine in $CCl_4$ solution.

angular term can override the distance term and result in anomalously small (but not necessarily with reversed sign) deshielding effects (17).

Support for the assignments and complexation model for 2,4-dimethoxypyrimidine was obtained from similar studies of the effect of Eu(fod)$_3$ on 6-chloro-2,4-dimethoxypyrimidine (**6**) (Fig. 4) where the presence of the chloro substituent was not found to alter the electronic character of the pyrimidine ring sufficiently to alter the mode of complexation. The C-2 methoxyl protons of **6** show the largest deshielding gradient (6.4 p.p.m.) (Fig. 4) whose somewhat smaller value than 7.8 p.p.m. for the C-2 methoxyl protons of 2,4-dimethoxypyrimidine cannot be attributed entirely to the electron withdrawing effect of the chloro substituent of **6** because the C-5 proton of both **3** and **6** shows the same gradient of 3.7 p.p.m. (Table 2).

In contrast to the above examples, no dif-

ferentiation is made between the 2 and 4 (or 6) methoxyl protons of 2,4,6-trimethoxypyrimidine (**5**) by $Eu(fod)_3$ in $CDCl_3$ solution (Fig. 5). In addition the C-5 proton of **5** shows a larger deshielding gradient (5.7 p.p.m.) (Table 2) than the methoxyl protons (4.3 p.p.m.) which suggests that a different complexation geometry may be involved with this molecule. In carbon tetrachloride solution Fig. 6, $Eu(fod)_3$ does permit one methoxyl group of *sym*-trimethoxypyrimidine (**5**) to be distinguished from the other two, but this distinction is only possible at higher molar concentrations of $Eu(fod)_3$ shift reagent, i.e. $>0.1\ M$ $Eu(fod)_3$/substrate. In this instance because the peak integrating for three protons consistently occurred upfield from the peak integrating for six protons, the former was assigned to the C-2 methoxyl group and complexation was assumed to involve either the C-4 or -6 methoxyl oxygen atom consistent with the large gradient (6.0 p.p.m.) for the C-5 proton of *sym*-trimethoxypyrimidine in $CCl_4$ solution.

It is apparent from these studies of the effect of various solvents and of the shift reagent, $Eu(fod)_3$, in model pyrimidines (**3**–**6**) for the novel methoxylated pyrimidones **1** and **2** that very subtle effects are involved which make the choice of model compounds difficult. From these studies, it appears that the structural evidence presented for the pyrimidones **1***a* and **2***a* is best considered on its own merits and internal consistency.

## Experimental

*Proton Magnetic Resonance Studies*

The p.m.r. shifts were measured with a Varian A-60A spectrometer with a probe temperature of 40°. The shifts are believed accurate to $\pm 0.02$ p.p.m.

The $Eu(fod)_3$ shift reagent was obtained from Merck Sharp and Dohme Canada Limited, P.O. Box 898, Pointe Claire–Dorval 700, Quebec.

*Syntheses*

The conditions for barbiturate synthesis and various physicochemical properties of 1-ethyl-5-methylbarbituric acid (**1**) have been described (18).

*1,5-Diethylbarbituric Acid (**2**)*

Diethyl ethylmalonate (20.0 g, 0.107 mol, $n_d^{20}$ 1.4164, Aldrich) was condensed with ethylurea (9.5 g, 0.110 mol, m.p. 92–94 °C, Aldrich) during 3 h heating under reflux in absolute ethanol (150 ml) containing dissolved sodium (5.0 g, 0.221 mol). The reaction mixture was diluted with water (200 ml), acidified with concentrated hydrochloric acid to Congo red, and left to crystallize overnight in a refrigerator. The crude dry solid (9.2 g, 50%) was recrystallized twice from boiling heptane containing sufficient benzene to maintain miscibility of the oily solute to obtain the analytical sample, m.p. 89.2–91.5° (precision m.p., ref. 19).

Anal. Calcd. for $C_8H_{12}N_2O_3$: C, 52.17; 6.57; N, 15.21. Found: C, 51.96, 52.03; H, 6.45, 6.43; N, 15.37, 15.42.

The p.m.r. spectrum: $\delta$ in $CDCl_3$ relative to TMS internal reference: 0.97 (t), $CH_3$ (C—Et); 1.20 (t), $CH_3$(N—Et); 2.18 (m) $CH_2$ (C—Et); 3.45 (t), CH (C-5); 3.93 (q), $CH_2$(N—Et); 9.32 (broad), NH.

*1-Ethyl-1,6-dihydro-2,4-dimethoxy-5-methyl-6-oxopyrimidine (**1***a*)*

Treatment of a methanolic solution of 1-ethyl-5-methylbarbituric acid (**1**) (m.p. 146.8–147.5 °C) with excess ethereal diazomethane (20) at 0–5 °C and subsequent evaporation gave an oil which crystallized on standing. The crude solid (m.p. 71–80 °C, 15% yield) was recrystallized twice from heptane to obtain an analytical sample of **1***a*, m.p. 80.5–82.2°(corr.) (19).

Anal. Calcd. for $C_9H_{14}N_2O_3$: C, 54.54; H, 7.11; N, 14.13. Found: C, 54.99, 55.29; H, 7.23, 7.30; N, 14.53, 14.51.

*1,5-Diethyl-1,6-dihydro-2,4-dimethoxy-6-oxopyrimidine (**2***a*)*

Similar treatment and handling of a methanolic solution of 1,5-diethylbarbituric acid (**2**) (m.p. 89.2–91.5 °C) gave a crude solid (m.p. 76–81 °C, 28% yield). Two recrystallizations from heptane gave the analytical sample of **2***a* (m.p. 85.6–87.2 °C (corr.) (19).

Anal. Calcd. for $C_{10}H_{16}N_2O_3$: C, 56.59; H, 7.60; N, 13.20. Found: C, 56.32, 56.33; H, 7.54, 7.45; N, 13.25, 13.30.

The p.m.r. spectrometry indicated the mother liquor fractions from both reactions using diazomethane to be complex mixtures of *O*,*N*-dimethyl and *O*,*O*-dimethyl positional isomers.

*Methoxylated Pyrimidines*

2,4-Dimethoxypyrimidine (**3**) and 6-chloro-2,4-dimethoxypyrimidine (**6**) were used as received from the Aldrich Chemical Co.

*4,6-Dimethoxypyrimidine (**4**)*

A methanolic solution (25 ml) of 4,6-dichloropyrimidine (10.0 g, 0.067 mol, Aldrich) was added in small portions to a freshly prepared methanolic solution of sodium methoxide (4.50 g, 0.20 mol Na/75 ml methanol). The exothermic reaction was allowed to proceed just below the boiling point of the mixture. The reaction mixture was allowed to cool to room temperature before the sodium chloride by-product was removed by filtration. The filtrate was stripped of methanol, and the resulting oil was distilled at reduced pressure to obtain liquid b.p. 36–40°/0.2 mm; lit. b.p. 85°/16 mm (21). The product was verified by p.m.r. spectral analysis (Table 3).

*2,4,6-Trimethoxypyrimidine (**5**)*

A methanolic solution (25 ml) of 2,4,6-trichloropyrimidine (5.0 g, 0.027 mol, Aldrich) was added in small portions to a freshly prepared methanolic solution of sodium methoxide (2.55 g, 0.108 mol Na/50 ml methanol). The reaction proceeded with bubbling and the evolution of heat. The

mixture was allowed to cool to room temperature before the precipitated sodium chloride was removed by filtration. The filtrate was reduced to an oil by rotary evaporation. The oil crystallized on standing. Three recrystallizations of the solid from heptane gave crystals (0.9 g) m.p. 50–52°; lit. m.p. 53° (22). The product was verified by p.m.r. spectral analysis (Table 3).

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