THE OPTICAL RESOLUTION OF 1-ARYL-4,6-DIMETHYL-2(1H)-PYRIMIDINONES

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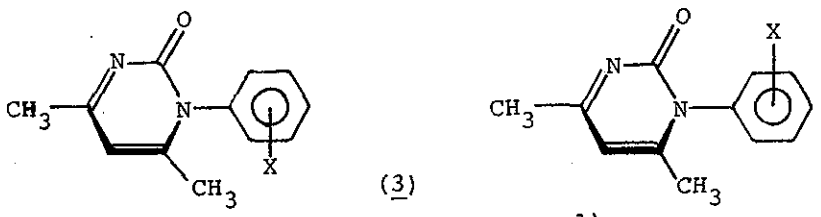
By the recrystallization of the salts with d-camphor-10-sulfonic acid, ortho substituted 1-aryl-4,6-dimethyl-2(1H)-pyrimidinones could succeed to separate the atropisomers.

It is well known that nucleosides contain D-ribose or 2-deoxy-D-ribose on the N-atom of the bases such as thymine, uracil, and cytosine. As the model compounds of the nucleosides, we have investigated the properties and reactivities of 1-aryl-4,6-dimethyl-2(1H)-pyrimidinones. The previous paper reported that methyl protons at the C-6 position were shifted to high field in nmr spectrum by the anisotropic



(3)

effect of an aryl group at the N-position.[1] This fact suggested that the pyrimidinone ring was perpendicular to the aryl ring in the most stable conformation of 1-aryl-4,6-dimethyl-2(1H)-pyrimidinones. Furthermore, the rotation barrier between two rings of 1-phenyl-4,6-dimethyl-2(1H)-pyrimidinone (3-a) was calculated to be ca. 30 kcal/mol by the MINDO/2 method. This rotation barrier is expected to be enough to separate the atropisomers. Thus, we tried to separate the atropisomers of the 1-aryl-4,6-dimethyl-2(1H)-pyrimidinones (3) by the optical resolution method.

The racemic 3 were synthesized by the condensation of acetylacetone (2) with N-arylureas (1),[2] which were prepared from the corresponding anilines and sodium cyanate. Since the pK_a of 1-phenyl-4,6-dimethyl-2(1H)-pyrimidinone hydrochloride was measured to be ca. 3.3 by uv spectral method, d-camphor-10-sulfonic acid (4) was used as the resolving agent. A mixture of 3 and 4 in ethanol was refluxed for an hour, then the resulting salt was recrystallized from ethyl acetate hexane mixture. After neutralization with aqueous sodium hydroxide, the specific rotation of the free bases was measured by a Union OR-50D desital polarimeter.

Table 1

The Specific Rotations of 1-Aryl-4,6-dimethyl-2(1H)-pyrimidinones (3)

Compound	Substituent (X)	Concn.*	$[\alpha]_D^{25}$**
3-a	H	---	-----
3-b	m-CH_3	0.6	0°
3-c	m-OCH_3	0.8	0°
3-d	m-Cl	0.8	0°
3-e	o-CH_3	0.6	-6.2°
3-f	o-Cl	0.8	-1.4°
3-g	o-OCH_3	0.8	+0.4°
3-h	o-OCH_2CH_3	1.0	+2.6°
3-i	o-CH_2CH_3	0.5	+4.5°

* Grams per 100 ml.

** All measurements were carried out in methanol.

Although the meta substituted pyrimidinones, 3-b, 3-c, and 3-d, exhibited no specific rotations, the ortho substituted derivatives, 3-e, 3-f, 3-g, 3-h and 3-i, showed specific rotations, listed in Table 1. The absolute rotation of 3-e was calculated about -120° at D-line from the result of the nmr spectrum in the presence of chiral shift reagent [Eu(tfc)$_3$].

Further, the activation parameter in the racemization of compound 3-e in methanol was given to be Ea = 32.9 kcal/mol, $\Delta G^{\ddagger}$ = 30.1 kcal/mol, $\Delta H^{\ddagger}$ = 32.1 kcal/mol, $\Delta S^{\ddagger}$ = 5.3 e.u.. From these results, it is concluded that the atropisomers of 1-aryl-4,6-dimethyl-2(1H)-pyrimidinones are possible to separate. Now the further study about the activation energy of the racemization of various 1-aryl-4,6-dimethyl-2(1H)-pyrimidinones is in progress by the kinetic method and the force field calculation.

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