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A STABLE ATROPISOMER OF 2,2',6,6'-TETRAMETHOXY-3,3'-DICARBOXYBIPHENYL AND OPTICAL RESOLUTION OF 2,2',6-TRIMETHOXY-3-CARBOXYBIPHENYL

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2,2',6,6'-Tetramethoxy-3,3'-dicarboxybiphenyl (I) has been reported[1] to be non-resolvable because four methoxy-groups were considered inadequate for obtaining restricted rotation and this fact is generally accepted.[2] However, the fact was considered to be inconsistent with the isolation of optically active biflavonyls belonging to the cupressuflavone,[3] amentoflavone,[4] and agathisflavone[5,6] series. These observations compelled us to reinvestigate the resolution of I.

Racemic I was prepared by the reported method[1] showing m.p. 239-240° (uncor.) (lit.[1] 231-232°) and its structure was confirmed by elemental analysis and spectral data. The dimethyl ester of I melted at 138-139° (uncor.) (from ethyl acetate). A brucine salt of I was easily obtained and showed m.p. 203-204° (decomp.) after three time recrystallizations from ethanol. Decomposition of the salt with acid gave an optically active acid, m.p. 183-184° (uncor.) (from ethyl acetate), $[\alpha]_D^{22}$ -18.5° and $[\alpha]_{400}^{22}$ -31.5° (c, 5, $CHCl_3$). An optically active dimethyl ester (noncrystalline) was obtained by methylation of the active acid with diazomethane and showed $[\alpha]_D^{23}$ +10.5° and $[\alpha]_{400}^{23}$ +29.5° (c, 5, $CHCl_3$). A chiral NMR-shift reagent, tris [3-(heptafluoropropylhydroxymethylene)-*d*-camphorato] europium(III),[7] was used for the determination of optical purity of the active ester and showed a satisfactory resolution, while inactive ester showed two sets of signals as given in the Table 1. When treated with boiling 0.5 *N*-ethanolic potassium hydroxide the (+)-ester was hydrolyzed to give (-)-acid, identical in rotation with the starting acid. Racemization was not noticeable ($[\alpha]_D$ and PMR spectra with the chiral shift reagent) after keeping the active acid for ten hours in a boiling acetic acid solution, nor after keeping the active ester for ninety minutes at 215° in a β-phenylethanol solution. This stability of the active acid (I) is much different from the reported facts.[1]

Table 1. δ-Values (ppm)[a] of dimethyl ester of I

Protons	Active or inactive ester without S.R.	Active (+)-ester with 0.46 equiv. of S.R.	Inactive ester with 0.32 equiv. of S.R.	
OMe	3.52 s	4.33	3.87[b]	4.05
	3.73 s	4.36	4.03[b]	4.08
COOMe	3.85 s	6.25	4.86	5.37[b]
H-arom.	6.75 d (J=9 Hz)	7.64	7.17	7.28[b]
	7.95 d (J=9 Hz)	9.91	8.86	8.96[b]

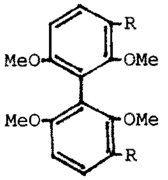
[a] PMR spectra were measured on a solution of 10-15 mg of ester in 0.5 ml of $CDCl_3$ using a JEOL PS-100 NMR spectrometer. [b] These are signals due to the (-)-ester. S.R. means the NMR-shift reagent cited in the text.[7]

In order to compare the optical stability of tetramethoxybiphenyl system with that of trimethoxybiphenyl system racemic 2,2',6-trimethoxy-3-carboxybiphenyl (II) was prepared by acetylation of 2,2',6-trimethoxybiphenyl[8] followed by oxidation with sodium hypochlorite solution, showing m.p. 157-158°. The methyl ester of II melted at 76-77°. The resolution of II was achieved through a brucine salt from acetone to give an optically active acid, m.p. 151-153°, $[\alpha]_D^{15}$ -12.3°, and $[\alpha]_{400}^{15}$ -58.5°(c, 1.3, $CHCl_3$). Its methyl ester: $[\alpha]_D^{15}$ -34.9° and $[\alpha]_{400}^{15}$ -112°(c, 1.2, $CHCl_3$). Complete racemization was observed when the β-phenylethanol solution of the active ester was kept at 125° for 15 min., indicating that the active ester is an optically labile compound. The half-lives of the active ester for racemization in dioxane solution at various temperatures were estimated and given in the Table 2.

Table 2. Racemization data of (-)-methyl ester of II in dioxane solution

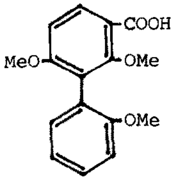
Temperature	$k \times 10^5 (sec^{-1})$	Half-life time
66.8°C	1.74	663 min.
77.4	6.06	191
88.2	27.2	42.5
101.0	88.6	13.0

E_{act} = 28.2 Kcal/mol (graphically calcd.)



I R=COOH

III R=NH_2



II

It has also been reported[1] that the dicamphorsulfonate salt of 2,2',6,6'-tetramethoxy-3,3'-diaminobiphenyl (III) showed mutarotation at -17°C. However, present work showed that III is also resolvable (m.p. 138-142°, $[\alpha]_D^{20}$ -92.8°). These findings indicating the larger steric size of methoxy-groups than reported earlier[1] may be explained partly by buttressing effects and partly by electronic repulsion effects. Some studies are now in progress to elucidate the steric effects of methoxy-groups and the discussions will be given in a full paper.

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