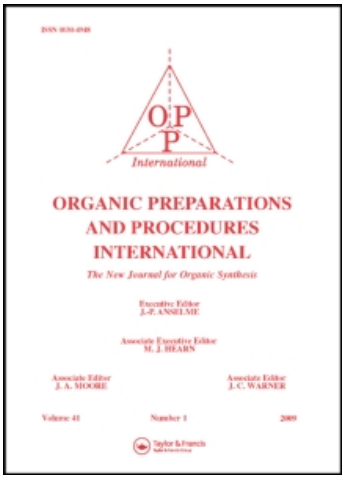


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# THE STUDIES ON DIHYDROISOCOUMARIN (III). THE SYNTHESIS OF 3-(3'-HYDROXY-4'-METHOXYPHENYL)-3,4-DIHYDROIROCOUMARIN

Y. Naoi[a]; K. Sakai[a]; T. Nakano[a]; H. Ito[a]; S. Higuchi[a]; T. Matsui[a]; Y. Takahashi[a]; S. Wagatsuma[a]; A. Nishi[a]; S. Sano[a]
[a] The Tokyo Research Laboratories, Yuki Gosei Kogyo Co., Ltd., Tokyo, Japan

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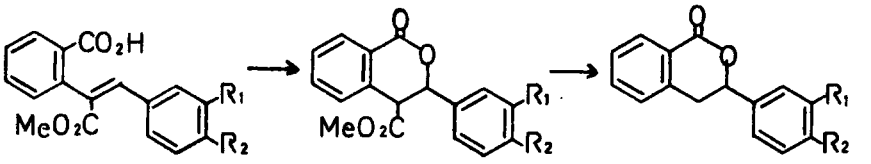
# THE STUDIES ON DIHYDROISOCOUMARIN (III). THE SYNTHESIS OF 3-(3'-HYDROXY-4'-METHOXYPHENYL)-3,4-DIHYDROISOCOUMARIN.

Y. Naoi, K. Sakai*, T. Nakano, H. Ito, S. Higuchi, T. Matsui, Y. Takahashi, S. Wagatsuma, A. Nishi and S. Sano

Yuki Gosei Kogyo Co., Ltd., The Tokyo Research Laboratories. 3-37-1, Sakashita, Itabashi-Ku, Tokyo, Japan, 174.



We have recently reported the preparation of stilbene dicarboxylic acids as useful precursors of phyllodulcin and hydrangenol[1], and now describe the preparation of 3-(3'-hydroxy-4'-methoxyphenyl)-3,4-dihydroisocoumarin (III, $R_1$ = OH, $R_2$ = OMe) from I ($R_1$ = $OCH_2Ph$, $R_2$ = OMe).




I II III

Application of the conditions of Pappo[2] and of Pinder[3] for synthesis of II ($R_1$ = OH, $R_2$ = OMe) gave so many products, that II ($R_1$ = OH, $R_2$ = OMe) could not be obtained satisfactorily. The smooth cyclization of I ($R_1$ = $OCH_2Ph$, $R_2$ = OMe) was achieved by reaction at 40-50° in $CHCl_3$ while HBr gas was bubbled through the solution for 4 hrs. and yielded readily separated products; 3-(3'-hydroxy-4'-methoxyphenyl)-4-carbomethoxy-3,4-dihydroisocoumarin (II,

$R_1$ = OH, $R_2$ = OMe) was isolated in 65 % yield and homophthalic acid and isovanillin were found as by-products. The decarboxylation of 3-(3'-hydroxy-4'-methoxyphenyl)-4-carbomethoxy-3,4-dihydroisocoumarin with water at 165° in an autoclave yielded 3-(3'-hydroxy-4'-methoxyphenyl)-3,4-dihydroisocoumarin in 21 % yield[4]; homophthalic acid and isovanillin were also obtained. The 3-aryl group of III is assigned to be in the axial position on the basis of the magnitude of the coupling constants between $H_3$ and the two hydrogens at C-4. The observed values $J_{AX}$ = 5 Hz and $J_{BX}$ = 9-10 Hz are consistent with a dihedral angle of 40° ($H_3$ and $H_4$) and 170° ($H_3$ and $H_4$) as shown by Dreiding model.

## EXPERIMENTAL

3-(3'-Hydroxy-4'-methoxyphenyl)-4-carbomethoxy-3,4-dihydroisocoumarin (II). - Through a solution of 10 g. (0.024 mole) of 2-carboxy-3'-benzyloxy-4'-methoxy-α-carbomethoxy stilbene[1] in 30-40 ml. of $CHCl_3$ was bubbled hydrogen bromide gas at 40-50° for 4 hrs. The reaction mixture was evaporated in vacuo, then 50-100 ml. of ether was added to the residue. The white crystals which precipitated were recrystallized from methanol to yield 5.5 g. (70 %) of white plates, mp. 163-164°.

IR: 1745 $cm^{-1}$ (ester C = O), 1720 $cm^{-1}$ (lactone C = O).

NMR (DMSO-$d_6$): τ = 3.75 ($H_3$, d), 4.3 ($H_4$, d), J = 8 Hz.

Mass Spectrum: m/e 328 ($M^+$).

Anal. Calcd. for $C_{18}H_{16}O_6$: C, 65.85; H, 4.91.

Found: C, 65.65; H, 5.14.

3-(3'-Hydroxy-4'-methoxyphenyl)-3,4-dihydroisocoumarin (III).

Twenty grams (0.061 mole) of 3-(3'-hydroxy-4'-methoxyphenyl)-4-carbomethoxy-3,4-dihydroisocoumarin was stirred with 200 ml. of water in 500 ml. autoclave at 165° for 10 hrs. After reaction, the presence of $CO_2$ gas was detected with saturated $Ba(OH)_2$ solution, and the autoclave was opened. The reaction mixture was evaporated in vacuo and the residue was chromatographed on alumina (solvent: benzene/methanol = 10/3). The first fraction was 3-(3'-hydroxy-4'-methoxyphenyl)-3,4-dihydroisocoumarin, which was recrystallized from benzene to yield 4.3 g. (21 %) of plates, mp. 142.5-143.5°.

IR: 3500 $cm^{-1}$ (OH), 1704 $cm^{-1}$ (lactone C = O).

NMR (DMSO-$d_6$): $\tau$ = 4.5 ($H_3$, q), $\tau$ = 6.7 ($H_4$, q), $J_{AB}$ = 18 Hz, $J_{AX}$ = 5 Hz, $J_{BX}$ = 10 Hz.

Mass Spectrum: m/e 270 ($M^+$).

Anal. Calcd. for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22.
Found: C, 71.33; H, 5.59.

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## REFERENCES

*To whom inquiries should be directed.

1. Y. Naoi, H. Ito, T. Nakano, S. Higuchi, K. Sakai, T. Matsui, S. Wagatsuma, Y. Takahashi, A. Nishi and S. Sano, Org. Prep. Proc. Int., 5, 81 (1973); Y. Naoi, S. Higuchi, Y. Takahashi, H. Ito, T. Nakano, T. Matsui, S. Wagatsuma, A. Nishi, S. Sano and K. Sakai, 17th Symposium on the Chemistry of Natural Products, p. 360 (Tokyo, 1973).

2. H. J. E. Lowental and R. Pappo, J. Chem. Soc., 1952, 4799.

3. J. B. Jones and A. R. Pinder, ibid., 1958, 2612.

4. M. Yamato, K. Hasigaki, Y. Kuwano and T. Koyama, Yakugaku Zasshi, 92, 535 (1972).

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