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A New Synthesis of Tephrosic Acid*1

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2′-Carboethoxymethoxy-4′,5′-dimethoxy-7-hydroxyisoflavone was prepared from 7-benzyloxy-4′,5′-dimethoxy-2′-hydroxyisoflavone *via* the corresponding 2′-carboethoxymethoxyisoflavone. The hydrolysis of the 7-hydroxyisoflavone with dilute alkali gave tephrosic acid (2,4-dihydroxyphenyl 2-carboxymethoxy-4,5-dimethoxybenzyl ketone) in a good yield.

Tephrosic acid (I) is an important intermediate in synthesizing rotenoids (*e. g.*, elliptone (II) and munduserone (III)). This acid, I, has been prepared from resorcinol and ethyl (2-cyanomethyl-4,5-dimethoxyphenoxy)acetate (IV) by the Hoesch reaction.[1] However, the preparation of the ester IV has been found to be disadvantageous because of either a poor over-all yield or the tediousness of separating an intermediate difficult to crystallize. The present paper will describe a convenient method of synthesizing I from 7-benzyloxy-4′,5′-dimethoxy-2′-hydroxyisoflavone (V)[2] according to a modification of a procedure reported earlier by the present

*1 The results of this investigation were presented at the 20th Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1967.

1) A. Robertson, *J. Chem. Soc.*, **1932**, 1163.

2) K. Fukui, M. Nakayama, T. Harano and H. Tsuge, 10th Symposium on the Chemistry of Natural Products, Symposium Papers, Tokyo (Oct., 1966), p. 145; K. Fukui, M. Nakayama and T. Harano, This Bulletin, **42**, 233 (1969).

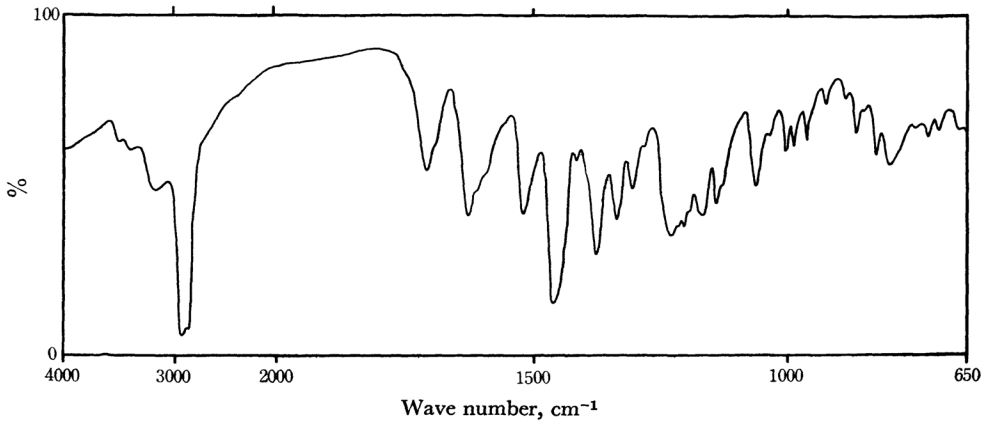
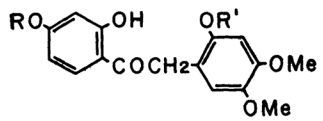
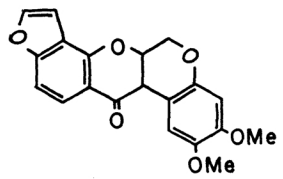


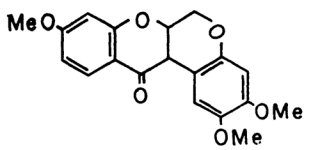
Fig. 1. IR spectrum of I (Nujol).



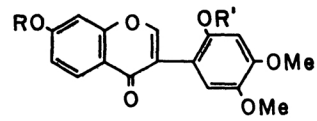
I R = H R' = CH_2CO_2H
VIII R = R' = Me
IX R = Me R' = CH_2CO_2Me
X R = Me R' = CH_2CO_2H



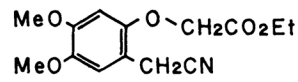
II



III



V R = $C_6H_5CH_2$ R' = H
VI R = $C_6H_5CH_2$ R' = CH_2CO_2Et
VII R = H R' = CH_2CO_2Et



IV

authors[3] and also be Chandrashekar *et al.*[4]

The reaction of the 2'-hydroxyisoflavone V with ethyl bromoacetate in the presence of anhydrous potassium carbonate afforded 7-benzyloxy-2'-carboethoxymethoxy-4',5'-dimethoxyisoflavone (VI) in a good yield. By catalytic hydrogenolysis over palladium-charcoal, the 7-benzyloxyisoflavone VI gave 2'-carboethoxymethoxy-4',5'-dimethoxy-7-hydroxyisoflavone (VII), which was then easily converted into its monoacetate by conventional methods. The treatment of VII with alcoholic potassium hydroxide gave the desired acid, I, in a good yield. This was identified with an authentic

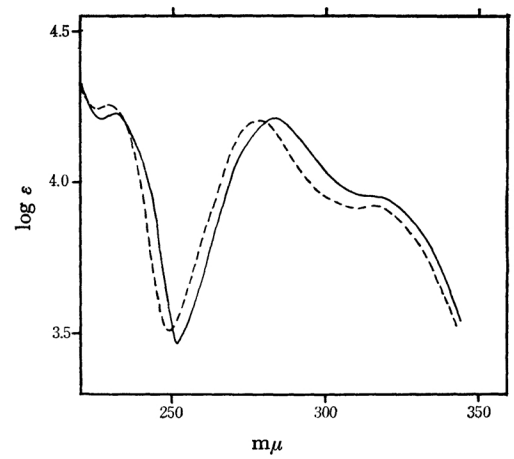


Fig. 2. UV spectra of I (——) and IX (------) in ethanol.

3) K. Fukui, M. Nakayama and T. Harano, *Experientia*, **23**, 613 (1967).

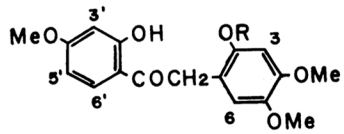
4) V. Chandrashekar, M. Krishnamurti and T. R. Seshadri, *Tetrahedron*, **23**, 2505 (1967).

specimen[5] by a mixed-melting-point determination and by infrared and ultraviolet spectral comparisons (Figs. 1 and 2).

The partial methylation of the acid I with diazomethane gave a methyl ester. A comparison of the NMR spectrum of the ester with that of the 2-hydroxy-4-methoxyphenyl 2,4,5-trimethoxybenzyl ketone (VIII)[6] (Table 1) indicated that the methylated specimen should be represented as 2-hydroxy-4-methoxyphenyl 2-carbomethoxymethoxy-4,5-dimethoxybenzyl ketone (IX). Finally, the hydrolysis of IX with dilute alkali gave tephrosic acid monomethyl ether (X), which had previously been obtained by an alternative route.[3]

Since the synthesis of (±)-II from I has already been carried out,[5] this paper completes the presentation of a new synthesis of (±)-II.

Table 1. The NMR spectra of 2-hydroxyphenyl benzyl ketones VIII and IX*



Compound	VIII R=Me	IX R=CH_2CO_2Me
Arom. C_3–H	6.55 s	6.49 s
C_6–H	6.75 s	6.75 s
$C_{3'}$–H	6.40 d	3.68 d
$C_{5'}$–H	6.40 q	6.47 q
$C_{6'}$–H	7.84 d′	7.94 d′
Ar.–CH_2–CO–Ar.	4.17 s	4.29 s
Ar.–O–CH_2–CO_2Me		4.62 s
Ar. –OMe and –CO_2Me	3.82 (3H)	3.75 (3H)
	3.85 (6H)	3.85 (9H)
	3.90 (3H)	
OH	12.68	12.67

* The NMR spectra were measured with a Hitachi Model R-20 NMR spectrometer (60 MHz), using tetramethylsilane as an internal standard (δ-values in $CDCl_3$; s, singlet; d, doublet (J_{meta} 2 Hz); d′, doublet (J_{ortho} 9 Hz); q, quartet (J_{meta} 2 Hz; J_{ortho} 9 Hz).

Experimental*2

7-Benzyloxy-2′-carboethoxymethoxy-4′,5′-dimethoxyisoflavone (VI). To a solution of isoflavone (V: mp 172—173°C)[2] (400 mg) and ethyl bromoacetate (200 mg) in anhydrous acetone (50 m*l*), anhydrous potassium carbonate (1.5 g) was added; the mixture was then refluxed for 24 hr. After the inorganic salts had been filtered off, the solution was concentrated to 5 m*l* and then diluted with water. The separated solid was collected and recrystallized from ethanol to give VI as colorless needles, mp 112—113°C; yield, 370 mg (77%). IR: 1736, 1640, 1620 cm^{-1} (C=O). UV: λ_{max} mμ (log ε); 248 (4.39), 296 (4.29).

Found: C, 68.38; H, 5.27%. Calcd for $C_{28}H_{26}O_8$: C, 68.57; H, 5.30%.

2′-Carboethoxymethoxy-4′,5′-dimethoxy-7-hydroxyisoflavone (VII). A solution of VI (320 mg) in ethyl acetate (100 m*l*) was submitted to catalytic hydrogenolysis at room temperature in the presence of Pd-C (10%: 90 mg). After the catalyst had been filtered off, the filtrate was evaporated under a vacuum; the residue was then recrystallized from ethanol to give VII as colorless microneedles, mp 217.5—218.5°C (lit.[7] mp 217—218°C); yield, 240 mg (92%). IR: 3250 (OH), 1735, 1633 cm^{-1} (C=O). UV: λ_{max} mμ (log ε); 255 (4.53), 296.5 (4.28), 336 (4.01).

Found: C, 63.08; H, 5.13%. Calcd for $C_{21}H_{20}O_8$: C, 62.99; H, 5.04%.

The acetate: acetic anhydride-anhydrous sodium acetate method; mp 137—138°C (colorless microneedles from ethanol). IR: 1768, 1733, 1655, 1625 cm^{-1} (C=O). UV: λ_{max} mμ (log ε); 294 (4.12).

Found: C, 62.19; H, 4.93%. Calcd for $C_{23}H_{22}O_9$: C, 62.44; H, 5.01%.

Tephrosic Acid (2,4-Dihydroxyphenyl 2-Carboxymethoxy-4,5-dimethoxybenzyl Ketone) (I). To a solution of VII (200 mg) in ethanol (50 m*l*), a 10% aqueous potassium hydroxide solution (20 m*l*) was added; the mixture was then refluxed for 2 hr. After the solvent had been removed as much as possible, the residue was acidified with 10% hydrochloric acid. The separated solid was collected and recrystallized from aqueous ethanol to give I as colorless microcrystals, mp 193—195°C (lit., mp 197°C,[1] mp 192.5—194°C,[5] mp 196°C[8]); yield, 100 mg (56%). It gave a reddish-brown color with an alcoholic ferric chloride solution. IR: 3530, 3430, 3230 (OH), 1715, 1638 cm^{-1} (C=O). UV: λ_{max} mμ (log ε); 231 (4.22), 282 (4.21), 314$_i$ (3.96).*3

Found: C, 58.07; H, 5.37%. Calcd for $C_{18}H_{18}O_8 \cdot \frac{1}{2}H_2O$: C, 58.22; H, 5.15%.

2-Hydroxy-4-methoxyphenyl 2-Carbomethoxymethoxy 4,5-dimethoxybenzyl Ketone (IX). I (25 mg) in ether (30 m*l*) was treated with an excess of diazomethane in ether. After standing at room temperature for 24 hr, the mixture was evaporated under a vacuum to dryness. The residue was recrystallized from ethanol to give IX as colorless needles, mp 125—126°C; yield, 25 mg (94%). It gave a reddish-brown color with an alcoholic ferric chloride solution. IR: 1740, 1635 cm^{-1} (C=O). UV: λ_{max} mμ (log ε): 229 (4.25), 278 (4.20), 316 (3.92).

Found: C, 61.62; H, 5.57%. Calcd for $C_{20}H_{22}O_8$: C, 61.53; H, 5.68%.

Tephrosic Acid Monomethyl Ether (2-Hydroxy-4-methoxyphenyl 2-Carboxymethoxy-4,5-dimeth-

5) H. Fukami, G. Sakata and M. Nakajima, *Agr. Biol. Chem.*, **29**, 82 (1965); the authentic sample of I was kindly supplied by Professor Hiroshi Fukami, Kyoto University.

6) K. Fukui, M. Nakayama, M. Hatanaka, T. Okamoto and Y. Kawase, This Bulletin, **36**, 397 (1960).

*2 All melting points are uncorrected; the infrared spectra were measured in Nujol, while the ultraviolet spectra were measured in ethanol.

7) H. Fukami, private communication.

8) E. P. Clark, *J. Am. Chem. Soc.*, **54**, 3000 (1932).

*3 i=inflection point.

oxybenzyl Ketone) (X). A mixtur of IX (10 mg), ethanol (10 m*l*), and a 10% aqueous potassium hydroxide solution (3 m*l*) was treated by a method similar to that used for I; mp 205—206°C (colorless microcrystals from ethanol) (lit. mp 206—207°C,[3] mp 205—206°C,[4] mp 204—205°C[9]). It gave a reddish-brown color with an alcoholic ferric chloride solution. IR: 3250 (broad) (OH), 1735, 1635 cm^{-1} (C=O). UV: λ_{max} mμ (log ε); 229.5 (4.27), 277 (4.24), 316 (3.97).

Found: C, 60.64; H, 5.28%. Calcd for $C_{19}H_{20}O_8$: C, 60.63; H, 5.36%.

9) N. Finch and W. D. Ollis, *Proc. Chem. Soc.*, **1960**, 176.

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