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SYNTHESIS OF ISOEUPARIN, A BENZOFURAN EXTRACTIVE OF *TAGETES PATULA*

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Key Word Index—*Tagetes patula*; Compositae; isoeuparin; 4-hydroxydehydrotremetone; benzofurans; *o*-halogenophenolcuprous acetylide coupling.

Abstract—The structure of isoeuparin, a constituent isolated from seedlings of *Tagetes patula*, is confirmed by a short synthesis, involving reaction of cuprous isopropenylacetylide with 2,4-dihydroxy-3-iodoacetophenone.

INTRODUCTION

The isolation of a new benzofuran from the seedlings of *Tagetes patula* L. has just been reported in this Journal [1]. The proposed structure (**1**) for this product, named isoeuparin (4-hydroxydehydrotremetone) was based essentially on interpretation of the ^{1}H NMR spectrum. We report here a short synthesis which confirms the 5-acetyl-4-hydroxy-2-isopropenylbenzofuran (**1**) structure.

RESULTS AND DISCUSSION

We have previously reported [2] the synthesis of the related natural 5-acetyl-2-isopropenylbenzofurans [euparin (**2**), dehydrotremetone and methoxyeuparin] by the reaction of cuprous isopropenylacetylide with an appropriate *o*-halogenophenol. Based on this method of benzofuran heterocycle construction, a preferred starting material for isoeuparin is 2,4-dihydroxy-3-iodoacetophenone (**4**). We found previously [3] that attempted mono-iodination of 2,4-dihydroxyacetophenone (**3**) gave mixtures of the 3-monoiodo (**4**), 5-monoiodo (**5**) and 3,5-di-iodo derivatives and that **5** was readily converted to euparin (**2**). A specimen of the 3-monoiodo derivative (**4**), obtained by iodination of **3** in di-isopropylamine–methanol solution and readily separated from the product mixture, was here employed. A simpler preparation of **4** has also been reported [4] and we have confirmed that the 3-iodo isomer is obtained in excellent yield by iodination of **3** in aqueous ethanol in the presence of iodic acid.

By heating **4** in pyridine solution with cuprous isopropenylacetylide, 5-acetyl-4-hydroxy-2-isopropenylbenzofuran (**1**) was readily obtained with constants in excellent agreement with those reported for isoeuparin. The ^{13}C NMR spectra for both isoeuparin (**1**) and euparin (**2**) are recorded in Table 1, with assignments based on the reported values for benzofuran [5] and additivity relationship of *o*-hydroxyacetophenone and benzene.

EXPERIMENTAL

2,4-Dihydroxy-3-iodoacetophenone (**4**). (a) Iodine (1.024 g; 0.004 mole) was added to a soln of 2,4-dihydroxyacetophenone (1.522 g; 0.01 mole) in EtOH (30 ml), followed by a soln of iodic acid (0.352 g; 0.002 mole) in H_2O (8 ml), and the mixture stirred at room temp. for 2 hr. It was then diluted with H_2O (to 250 ml) and the ppt (pink solid, 2.34 g, mp 140–162°) collected, and crystallized from hexane to give the 3-iodo compound (**4**) as beige needles, mp 158–162° (softens at 140°); ^{1}H NMR (Me_2CO-d_6): δ 2.60 (*s*, Ac), 6.62 (*d*, $J = 9$ Hz, H-5), 7.82 (*d*, $J = 9$ Hz, H-6) and 13.78 (*s*, OH). (b) A soln of iodine (1.66 g) in MeOH was added dropwise to a stirred soln of 2,4-dihydroxyacetophenone (970 mg) in di-isopropylamine (10 ml) and MeOH (20 ml) and the mixture stirred at room temp. for 22 hr. It was then poured into dil. HCl (1 N, 100 ml) and the ppt [315 mg, consisting of a mixture of the 3-iodo derivative (**4**), the 5-iodo derivative (**5**) and

Table 1. ^{13}C NMR spectral data of isoeuparin (**1**) and euparin (**2**)

Carbon	1	2
2	156.7*	157.9*
3	100.8	99.5†
4	158.5*	123.5
5	114.3†	121.9‡
6	127.3	159.6*
7	103.4	102.4†
8	159.5	161.5
9	118.9†	116.8‡
10	204.1	203.9
11	26.9	26.8
12	132.3	132.1
13	113.4	113.7
14	19.2	19.2

*†‡These values may be interchanged.

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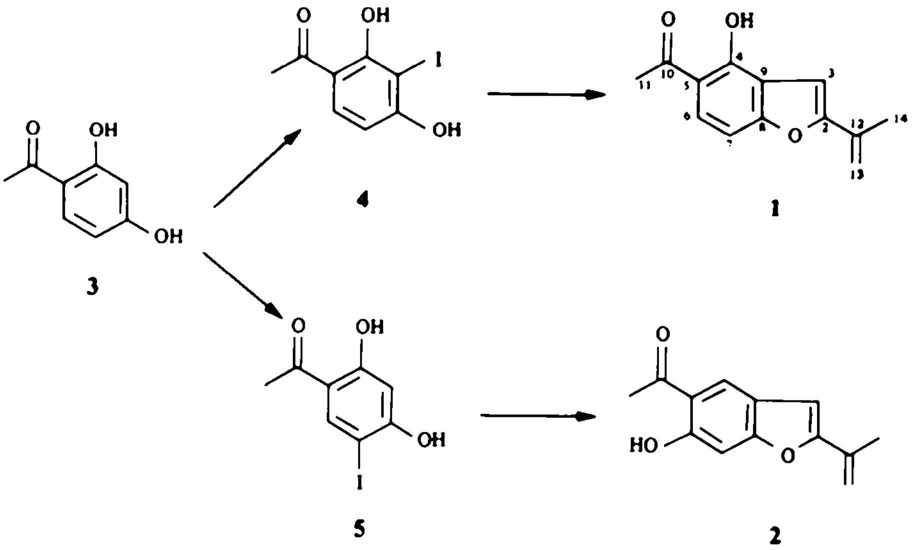

Scheme 1.

the 3,5-di-iodo derivative (6) in 1.4:1:4.8 ratio by ^{1}H NMR analysis] collected. Further dilution of the filtrate with H_2O (50 ml) yielded a ppt (pink solid, 200 mg) of the 3-iodo compound (4) identical with that obtained in (a).

5-Acetyl-4-hydroxy-2-isopropenylbenzofuran (*isoeuparin*, 1). A soln of 2,4-dihydroxyacetophenone (304 mg) in pyridine (12 ml) was added to a stirred mixture of cuprous isopropenylacetylide (165 mg) [2] in the same solvent (12 ml) and the mixture heated under reflux under nitrogen for 13 hr. It was then diluted with Et_2O (150 ml), cooled to 0° and filtered. Evaporation of the washed (3 × 100 ml H_2O and 1 × 100 ml brine) and dried organic layer gave a residual yellow-brown oily solid, which was boiled with *n*-hexane (10 ml with a drop of pyridine) for 5 min. The supernatant liquor was decanted from dark residual tar, and on cooling gave isoeuparin (1) as yellow needles (48 mg), mp 109–110° (lit. [1] mp 107–108°); ^{1}H NMR ($CDCl_3$): δ2.12 (*s*, vinyl Me), 2.65 (*s*, Ac), 5.19 (*s*, vinyl H), 5.76 (*s*, vinyl H), 6.84 (*s*, H-3), 7.00 (*d*, $J = 8$ Hz, H-7) and 7.64 (*d*, $J = 8$ Hz, H-6) and 13.25 (*s*, OH).

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