Synthesis of Naturally Occurring 5-Acetyl-2-isopropenylbenzofurans

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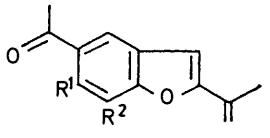
Euparin (1), dehydrotremetone (2), and methoxyeuparin (3) have been synthesized by a short procedure involving the reaction of copper(I) isopropenylacetylide with an appropriate *p*-acetyl-*o*-halogenophenol.

SEVERAL classes of natural products can be regarded as acetophenone derivatives bearing an isopentenyl residue either as a side-chain or as part of a heterocycle, and biogenetic relationships between them have been discussed.[1] One such class is based on the 5-acetyl-2-isopropenylbenzofuran framework and is exemplified by euparin (1), dehydrotremetone (2), and methoxyeuparin (3).

We have recently synthesized some natural norlignans with 5-alkyl-2-arylbenzofuran structures[2] and have since sought to determine if the acetophenone products were amenable to synthesis by the same general pathway of benzofuran construction[3-6] by reaction of an *o*-halogenophenol with copper(I) isopropenylacetylide.



(1) R^1 = OH, R^2 = H
(2) R^1 = R^2 = H
(3) R^1 = OH, R^2 = OMe

Euparin, a yellow constituent of *Eupatorium purpureum* (gravel root) has been known since 1890,[7] and its structure (1) was established by Robertson[8] in 1939. It has since been isolated from other *Eupatorium* species (*E. cannabinum*[9] and *E. japonica*[10]), from *Encelia californica*,[11] and from *Abrotanella nivigena*,[12] and its structure has been confirmed by two independent syntheses.[13,14] We considered that euparin (1) would be formed in one step by the reaction of copper(I) isopropenylacetylide (5) with 5'-bromo-2',4'-dihydroxyacetophenone (9). A copper salt of isopropenylacetylene (4) has been mentioned, without experimental detail, as an air-stable non-explosive yellow solid;[15] we have prepared the salt (5) readily from the acetylene (4) by treatment with copper sulphate and hydroxylamine hydrochloride in aqueous ethanolic ammonium hydroxide. The required bromophenol (9) was obtained in high yield from 2',4'-dihydroxyacetophenone (6) by acetylation to give the 4'-*O*-acetyl derivative[16,17] (7), conversion into the bromo-acetate[18] (8) by treatment with bromine in 80% acetic acid, and basic hydrolysis. Coupling of the bromophenol (9) with the salt (5) in pyridine then gave, in 42% yield, 5-acetyl-6-hydroxy-2-isopropenylbenzofuran (1), with spectroscopic data in excellent agreement with those reported for euparin.

Tremetol is the toxic principle of the weed *Eupatorium urticaefolium* (white snakeroot) responsible for the cattle illness 'trembles' and milk sickness in humans. From this source, Bonner[19] isolated three toxic ketones,

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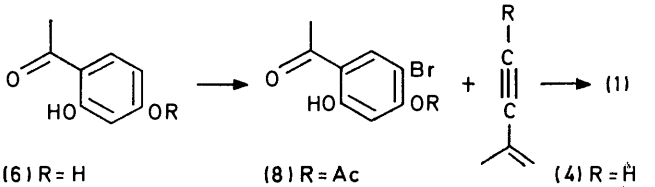
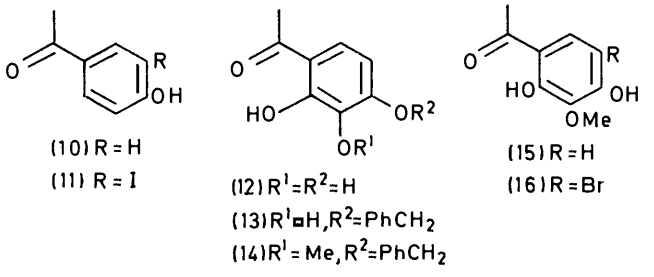
tremetone, dehydrotremetone, and hydroxytremetone, and showed [20] that dehydrotremetone was 5-acetyl-2-isopropenylbenzofuran (2). The same product has also been obtained from *Aplopappus heterophyllus* (rayless goldenrod) [21] and synthesized by the procedures used previously for euparin.[13,14] To synthesize dehydrotremetone by coupling with copper(I) isopropenylacetylide required an appropriately substituted monohalogeno-*p*-hydroxyacetophenone: the iodo-derivative (11) was readily obtained by iodination of the phenol (10) and when treated with the salt (5) gave dehydrotremetone (2).





From *Helianthella uniflora*, Bohlmann and Grenz [1] isolated several acetophenone derivatives, one of which was named methoxyeuparin and formulated, principally on the basis of spectroscopic data, as 5-acetyl-6-hydroxy-2-isopropenyl-7-methoxybenzofuran (3). This structure is now confirmed by a simple synthesis. The starting phenol (15) is known and readily prepared from 2′.3′.4′-trihydroxyacetophenone (12) by monobenzylation to give the 4-*O*-benzyl derivative (13) followed by monomethylation to give the 4-*O*-benzyl-3-*O*-methyl derivative (14) and hydrogenolysis.[22] The ^{1}H n.m.r. spectra are in full accord with these intermediate structures. Bromination of (15) in 80% acetic acid gave the 5′-bromo-derivative (16) which in the usual coupling reaction with the salt (5) gave methoxyeuparin (3), with spectroscopic data in agreement with those reported.

Changes occurring in the ^{1}H n.m.r. spectra of solutions of each of these isopropenylbenzofurans in [^{2}H]chloroform show that they are unstable. Since solutions in carbon tetrachloride show no comparable behaviour, we attribute the instability to sensitivity to traces of acids. In this connection, loss of material during recrystallization was minimized by addition of a few drops of pyridine to the solvents.

EXPERIMENTAL

N.m.r. spectra were determined for solutions in [^{2}H]-chloroform (unless otherwise stated), with tetramethylsilane as internal standard.

Copper(I) Isopropenylacetylide (5).—Hydroxylamine hydrochloride (10.51 g) was added to a stirred solution of copper sulphate pentahydrate (18.91 g) in concentrated ammonium hydroxide (76 ml) and water (300 ml) under nitrogen. After the deep blue colour had faded (*ca.* 10 min), a cloudy solution of isopropenylacetylene (5 g) in 95% ethanol (375 ml) was added rapidly with continued stirring, and the consequent bright yellow precipitate (5) was collected, washed with water, ethanol, and ether, and stored *in vacuo* (P_2O_5); yield 4.13 g, m.p. 120—200° (slow decomp.) [lit.,[15] m.p. 187—191° (decomp.)].

4′-Acetoxy-2′-hydroxyacetophenone (7).—A mixture of 2′,4′-dihydroxyacetophenone (6) (10 g), pyridine (50 ml), and acetic anhydride (6.30 ml) was heated on a steam-bath for 1 h, then cooled. Ice was added and the pale green precipitate (6.90 g) was crystallized once from aqueous methanol to give the acetate (7) as flakes, m.p. 69—71° (lit.,[16] 72—73°; lit.,[17] 75—76°); δ 2.30 (s, OAc), 2.60 (s, MeCO), 6.58—7.88 (m, ArH), and 12.47 (s, OH).

4′-Acetoxy-5′-bromo-2′-hydroxyacetophenone (8).—This was prepared as described; [18] m.p. 85°; δ 2.35 (s, OAc), 2.58 (s, COMe), 6.80 (s, H-3′), 7.94 (s, H-6′), and 12.27 (s, OH).

5′-Bromo-2′,4′-dihydroxyacetophenone (9).—To a solution of the acetate (8) (0.8 g) in methanol (45 ml) was added sodium hydroxide (1 g) in water (5 ml), and the mixture stirred overnight under nitrogen. It was then acidified with dilute sulphuric acid, and the precipitate was collected and boiled with acetone. The solution was filtered and evaporated to yield the bromophenol (520 mg), m.p. 165—170° (lit.,[18] 171°); δ [$(CD_3)_2CO$] 2.61 (s, COMe), 6.53 (s, H-3′), 8.05 (s, H-6′), 9.88br (s, 4′-OH), and 12.62 (s, 2′-OH).

5-Acetyl-6-hydroxy-2-isopropenylbenzofuran (*Euparin*) (1).—To a suspension of the copper salt (5) (144 mg) in pyridine (10 ml) was added a solution of the bromophenol (9) (231 mg) in the same solvent (10 ml), and the mixture heated under reflux (nitrogen atmosphere) for 22 h. It was then cooled, diluted with ether (200 ml), set aside at 0° C overnight, and filtered. The filtrate was washed with brine and water, treated with charcoal, dried ($MgSO_4$), and evaporated. Crystallization of the residue from aqueous methanol gave euparin (6) as yellow needles (92 mg), m.p. 118—120° (lit.,[8] 118.5—121°; lit.,[13,14] 121—122°), $\lambda_{max.}$ (EtOH) 238sh (14 000), 263 (35 100), 290.5 (14 500), 302 (11 200), and 358 nm (6 000); δ 2.08 (d, *J* 1 Hz, MeC=), 2.65 (s, COMe), 5.12—5.27 (m, vinylic H), 5.70—5.82 (m, vinylic H), 6.53 (s, H-3), 6.97 (s, H-7), 7.88 (s, H-4), and 12.53 (s, OH).

4′-Hydroxy-3′-iodoacetophenone (11).—To a solution of *p*-hydroxyacetophenone (10) (4.08 g) in concentrated ammonium hydroxide (250 ml) was added rapidly with stirring a solution of potassium iodide (24.2 g) and iodine (7.67 g) in water (60 ml). Stirring at room temperature was continued overnight (colour changed from black to cloudy orange), after which the mixture was filtered to give iodoform (346 mg), as yellow plates from methanol, m.p. 122—124.5°, δ [$(CD_3)_2CO$] 5.52 (s). The filtrate was concentrated

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and acidified with sulphuric acid to pH 1, and the precipitate (4.99 g) collected, dissolved in benzene, and treated with charcoal. Evaporation of the filtered solution and crystallization of the residue from aqueous methanol gave the crude iodophenol (11) as bright yellow needles (4.22 g). The yellow colour could not be removed by recrystallization, but t.l.c. [silica gel; benzene–acetone (9 : 2)] gave a band (R_F 0.44) which on elution afforded *4′-hydroxy-3′-iodoacetophenone* (11) as needles, m.p. 154—156° (with sintering) (Found: C, 37.1; H, 2.85. $C_8H_7IO_2$ requires C, 36.7; H, 2.7%); δ 2.51 (s, COMe), 7.07 (d, *J* 9 Hz, H-5′), 7.99 (dd, *J* 9 and 2.5 Hz, H-6′), and 8.40 (d, *J* 2.5 Hz, H-2′).

5-Acetyl-2-isopropenylbenzofuran (*Dehydrotremetone*) (2).—A mixture of the copper salt (5) (73 mg) and the crude iodophenol (11) (131 mg) in pyridine (20 ml) was treated and worked up as for euparin. Crystallization of the product (84.5 mg) from aqueous methanol gave dehydrotremetone as flakes (42 mg), m.p. 82.5—83.5° (lit.,[19] 87.5—88.5; lit.,[21] 80—82°; lit.,[14] 83—85°), $\lambda_{max.}$ (EtOH) 256 (ε 39 400), 282 (19 100), 286 (17 900), 295 (14 800), and 310 nm (4 600); δ 2.07 (d, *J* 1 Hz, MeC=), 2.57 (s, COMe), 5.12—5.27 (m, vinylic H), 5.73—5.85 (m, vinylic H), 6.60 (s, H-3), 7.38 (d, *J* 8 Hz, H-7), 7.88 (dd, *J* 8 and 2 Hz, H-6), and 8.08 (d, *J* 2 Hz, H-4).

4′-Benzyloxy-2′,3′-dihydroxyacetophenone (13).—Benzylation of 2′,3′,4′-trihydroxyacetophenone [23] (12) (14 g), δ [$(CD_3)_2CO$] 2.53 (s, COMe), 6.50 (d, *J* 9 Hz, H-5), 7.37 (d, 9 Hz, H-6), and 12.73 (s, 2-OH) as described [22] yielded the *O*-benzyl derivative (13) as yellow needles (8 g) (from methanol), m.p. 133—135° (lit.,[22] 137—138°); δ 2.50 (s, COMe), 5.18 (s, PhCH_2), 6.51 (d, *J* 9 Hz, H-5′), 7.22 (d, *J* 9 Hz, H-6′), 7.25—7.58 (m, ArH), and 12.56br (s, 2′-OH).

4′-Benzyloxy-2′-hydroxy-3′-methoxyacetophenone (14).—Prepared as described,[22] the ketone (14) had m.p. 143—145° (lit.,[22] 146°), δ 2.53 (s, COMe), 3.90 (s, OMe), 5.22 (s, PhCH_2), 6.51 (d, *J* 9 Hz, H-5′), 7.38br (s, ArH), 7.44 (d, *J* 9 Hz, H-6′), and 12.58 (s, 2′-OH).

2′,4′-Dihydroxy-3′-methoxyacetophenone (15).—Prepared from the *O*-benzyl derivative (14) by hydrogenolysis over palladium–carbon (5%) in ethyl acetate, the product (15) was obtained from aqueous methanol as flakes, m.p. 141—144° [lit.,[22] long needles, m.p. 76° (from same solvent)]; δ 2.55 (s, COMe), 3.97 (s, OMe), 6.52 (d, *J* 9 Hz, H-5′), 7.46 (d, *J* 9 Hz, H-6′), and 12.91 (s, 2′-OH).

5′-Bromo-2′,4′-dihydroxy-3′-methoxyacetophenone (16).—To a solution of the phenol (15) (1.45 g) in 80% acetic acid (25 ml) was added a solution of bromine (1.28 g) in acetic acid (5 ml) and the mixture was stirred overnight. It was then poured into water (200 ml) and the product collected, washed with water, and crystallized from methanol and aqueous methanol to yield the *bromophenol* (16) as pale yellow needles (1.33 g), m.p. 110.5—112.5° (Found: C, 41.2; H, 3.6. $C_9H_9BrO_4$ requires C, 41.4; H, 3.45%); δ 2.57 (s, COMe), 4.00 (s, OMe), 6.67br (s, 4′-OH), 7.68 (s, H-6′), and 12.71 (s, 2′-OH).

5-Acetyl-6-hydroxy-2-isopropenyl-7-methoxybenzofuran (*Methoxyeuparin*) (3).—A mixture of the copper salt (5) (81 mg) and the bromophenol (16) (131 mg) in pyridine (20 ml) was treated and worked up as for (1) and (2). Crystallization of the product from ether–light petroleum (with a few drops of pyridine) gave *methoxyeuparin* (45 mg), m.p. 92.5—93° (lit.,[1] 95—96°), $\lambda_{max.}$ (Et_2O) 237.5 (ε 12 600), 272.5 (35 500), and 362 nm (4 600); δ 2.08 (m, MeC=), 2.57 (s, COMe), 4.05 (s, OMe), 5.13 (m, vinylic H), 5.76 (m, vinylic H), 6.40 (s, H-3), 7.45 (s, H-4), and 12.38 (s, 6-OH).

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