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# PEREZONE AND RELATED SESQUITERPENES FROM PARVIFOLINE

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ABSTRACT.—The previously known sesquiterpenes, curcuhydroquinone [**5b**], curcuquinone [**6a**], xanthorrhizol [**5a**], perezone [**6c**], isoperezone [**6b**], and hydroxyperezone [**6d**] were obtained in good yields from parvifoline [**1**]. The chiral center in parvifoline is assigned the *R* configuration based on these conversions.

A large number of natural products containing the quinone functionality have shown useful chemotherapeutic activity (1,2). As a result of the utility of these compounds, intense synthetic efforts have been directed toward the development of methods that would permit construction of natural quinones (3-7) or the regioselective introduction of functionality into the quinone system. We wish to report the preparation of the benzoquinones perezone [**6c**] (8), isoperezone [**6b**] (9), hydroxyperezone [**6d**] (10), and curcuquinone [**6a**] (11), and the sesquiterpene xanthorrhizol [**5a**] (12) from parvifoline [**1**] (13,14), which was obtained as a major component (15%) of *Pereziae* spp. (15).

Parvifoline [**1**] can be isomerized by acid catalysis to isoparvifoline [**2**], the ozonolysis of which produces the aldehyde **3a**. This is a key compound for the preparation of the sesquiterpenes mentioned previously, since its aromatic ring has a methyl group *para* to the side chain. This side chain has a chiral center that is not involved in the synthetic pathways to those sesquiterpenes.

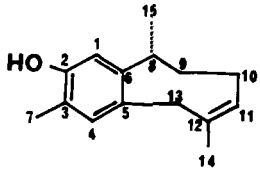
Treatment of **3a** by Dakin's reaction (16) gave hydroquinone **4a** and this, with $CH_3MgI$ (17) followed by dehydration, gave (−)-curcuhydroquinone [**5b**]. In agreement with the chemical correlation made by McEnroe (11), we obtained $[\alpha]^{25}D-36$ (*c* 2.3, $CHCl_3$) indicating that the previously unassigned stereochemistry of C-8 of parvifoline [**1**] (13) is the *R* configuration. Treatment of curcuhydroquinone [**5b**] with Jones reagent yielded curcuquinone [**6a**] (11), while **5b** by previously reported reaction with $H_2O_2$/NaOH yielded hydroxyperezone [**6d**] (18).

Oxidation (19) and decarboxylation (20) of aldehyde **3a** produced 5-(2′-ketoheptan-6′-yl)-2-methylphenol, which can also be prepared by direct decarbonylation of **3a** with Wilkinson's reagent (21,22). Reactions of this intermediate with $CH_3MgI$ followed by dehydration gave xanthorrhizol [**5a**], identical with the natural product (12).

Aldehyde **3a** with $Me_2SO_4$ produces methoxyaldehyde **3b**, which by a modification of Dakin's reaction (23) with catalytic $SeO_2$, afforded methoxyphenol **4b**. This compound with $CH_3MgI$ and dehydration gave 4-*O*-methylcurcuhydroquinone [**5c**]. Hydroxylation *ortho* to the free hydroxyl group with $Cu_2Cl_2$ in MeCN (24,25) occurs smoothly and in good yield to produce the corresponding catechol **5d**, which by oxidative demethylation (26) with $AgO/HNO_3$ produced isoperezone [**6b**] as previously reported.

Perezone [**6c**] was obtained by treatment of **3a** under the same conditions ($Cu_2Cl_2$/MeCN) (23) followed by Dakin's reaction (16) to give a hydroxyhydroquinone, which was not isolated. Grignard reaction with excess $CH_3MgI$ on this compound, dehydration, and subsequent oxidation gave perezone [**6c**] identical with the natural product (8).

As parvifoline [**1**] is easily obtained in very high yields from certain *Pereziae* spp. and can be easily functionalized, it can serve as a starting material for other sesquiterpenes having the same *R* configuration of the chiral center.



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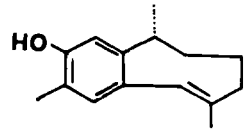

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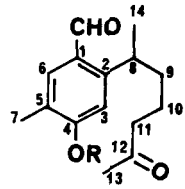
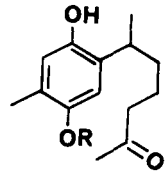
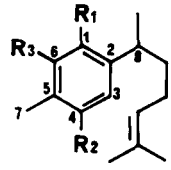


**3a** R=H
**3b** R=Me



**4a** R=H
**4b** R=Me



**5a** $R_1=R_2=H$, $R_3=OH$
**5b** $R_1=R_2=OH$, $R_3=H$
**5c** $R_1=OH$, $R_2=OMe$, $R_3=H$
**5d** $R_1=R_3=OH$, $R_2=OMe$

**6a** $R_1=R_2=H$
**6b** $R_1=H$, $R_2=OH$
**6c** $R_1=OH$, $R_2=H$
**6d** $R_1=R_2=OH$

## EXPERIMENTAL

Melting points are uncorrected. Ir spectra were carried out on a Perkin-Elmer 599B; $^1$H-nmr spectra were determined in $CDCl_3$ with internal TMS on a Varian Associates EM-360. Optical rotations, measured by using a Perkin-Elmer 121M polarimeter, were performed at room temperature. High resolution mass spectra were measured in a Finnigan MAT-311A.

PARVIFOLINE [**1**].—The dried and ground roots (1 kg) of *Pereziae longifolia* Blake (Compositae) were extracted twice with hexane (5 liters) under reflux for 4 h, and the combined extracts were evaporated to dryness. The solid obtained was recrystallized from $C_6H_6/Me_2CO$ to yield 138 g (13.8%) of parvifoline [**1**] identical in all respects with authentic samples (14).

ISOPARVIFOLINE [**2**].—A solution containing 100 g of parvifoline [**1**] and catalytic *p*-TsOH in $C_6H_6$ was heated at reflux for 3 h. The reaction mixture was washed (dilute $NaHCO_3$ and $H_2O$), dried ($Na_2SO_4$), and evaporated. The residue was chromatographed ($SiO_2$); elution with $C_6H_6$ yielded 99 g of isoparvifoline [**2**] as a colorless oily material that showed ir bands at 3500 (O-H) and 1650 $cm^{-1}$ (C=C); $^1$H nmr 5.56, 6.33, and 5.93 (1H each, s, H-1, H-4, and H-11), 5.00 (1H, broad s, OH), 2.93 (1H, CH), 2.13 (3H, s, $ArCH_3$), 1.81-1.23 (6H, m, $3\times CH_2$), 1.20 ppm (3H, d, $J$=7 Hz, $CH_3CH$); hrms *m/z* 216.1523 $M^+$ (calcd for $C_{15}H_{20}O$, 216.1514).

2(2′-KETOHEPTAN-6′-YL)-4-HYDROXY-5-METHYLBENZALDEHYDE [**3a**].—Isoparvifoline [**2**] (50 g) in EtOAc (200 ml) was treated with ozone at −70° until the characteristic blue color was obtained (12 h). The resultant solution was gradually added to a suspension of 35 g of powdered zinc and 300 ml of HOAc at 50%. After 1 h of agitation, the mixture was filtered under reduced pressure. The resultant solution was neutralized with 10% $NaHCO_3$, extracted with $Et_2O$, washed with $H_2O$, dried with $Na_2SO_4$, and evaporated to dryness to obtain a sticky oil that was purified by chromatography over $SiO_2$. Elution with $CHCl_3$-$Me_2CO$ (9.5:0.5), gave 48 g (96%) of the aldehyde **3a** as a colorless oil: ir 3400 (OH), 1710 (C=O ketone), 1680 $cm^{-1}$ (C=O aldehyde); $^1$H nmr 9.93 (1H, s, CHO), 7.45 and 6.75 (1H each, s, ArH), 8.51 (1H br, OH), 3.76 (1H, m, $J$=7 Hz, CH), 2.4 (2H br, $CH_2CO$), 2.23 and 2.10 (3H each, s, 7-$CH_3$ and 13-$CH_3$), 1.50 (4H, br, -$CH_2CH_2$-), 1.13 ppm (3H, d, $J$=7 Hz, $CH_3CH$); hrms *m/z* 248.1431 $M^+$ (calcd for $C_{15}H_{20}O_3$, 248.1412).

2(2′-KETOHEPTAN-6′-YL)-2-METHYL-1,4-HYDROQUINONE [**4a**].—To a solution containing 2.48 g of **3a** in 10 ml of 1N NaOH was added at room temperature 12 ml of 3% $H_2O_2$; the solution was kept in the dark at 40° during 15 h (16). The mixture was neutralized with HOAc and extracted with $Et_2O$, giving after evaporation the hydroquinone **4a** (2.3 g, 98%); ir 3400 (OH) and 1710 $cm^{-1}$ (C=O ketone); $^1H$ nmr 6.56 (2H, apparent s, ArH), 5.36 (2H, br, $D_2O$-exchangeable, ArOH), 3.02 (1H, m, $J$=7 Hz, CH), 2.41 (2H, br s, 11-$CH_2$), 2.13 (6H, s, 7- and 13-$CH_3$), 1.46 (4H, m, -$CH_2CH_2$-), 1.11 ppm (3H, d, $J$=7 Hz, $CH_3CH$); hrms *m/z* 236.1431 $M^+$ (calcd for $C_{14}H_{20}O_3$, 236.1412).

(−)-CURCUHYDROQUINONE [**5b**].—A solution of phenol **4a** (0.944 g, 4 mmol) in dry $Et_2O$ (50 ml) was added dropwise under anhydrous conditions to an ethereal solution of $CH_3MgI$ (2.33 g, 14 mmol). The mixture was agitated with warming to reflux during 3 h (17), hydrolyzed with 10% HCl, extracted twice with $Et_2O$, and evaporated to dryness. The crude product of the reaction was dissolved in 50 ml of $C_6H_6$ and treated with a catalytic quantity of $I_2$. After heating at reflux for 0.5 h, the solution was washed ($H_2O$) and evaporated to yield curcuhydroquinone [**5b**] (840 mg, 90%) as an oil, $[\alpha]^{25}D$ −36° (*c* 2.3, $CHCl_3$). Spectroscopic properties (uv, ir, and $^1H$ nmr) were identical to those reported (11). Curcuhydroquinone [**5b**] in $Me_2CO$ was treated with an excess of Jones reagent in the cold. After extraction with $Et_2O$, curcuquinone [**6a**] (11) was obtained in quantitative yield.

HYDROXYPEREZONE [**6d**].—A mixture of 17% $H_2O_2$ (2 ml) and 25% NaOH (2 ml) was added to 200 mg of curcuhydroquinone [**5b**]. The reaction mixture was stirred at room temperature overnight (18). After acidification with 10% HCl, extraction with EtOAc, drying ($Na_2SO_4$), and evaporation to dryness, the resulting orange-red plates, mp 121-123° (200 mg, 94%), were characterized as hydroxyperezone [**6d**] by comparison with an authentic sample (10).

XANTHORRHIZOL [**5a**].—The aldehyde **3a** (500 mg) was dissolved in $C_6H_6$ (25 ml) under $N_2$. Chlorotris (triphenylphosphine) rhodium (21,22) (620 mg) was added, and the solution warmed at 50° with stirring during 3 h. As the red color vanished from the rhodium complex, a solid light yellow precipitate was formed that was removed by filtration under reduced pressure. The filtrate was evaporated to dryness to give a yellow oil which was chromatographed on $SiO_2$. Elution with $CHCl_3$ afforded 400 mg of 5-(2′-ketoheptan-6′-yl)-2-methylphenol; ir 3400 (OH) and 1710 $cm^{-1}$ (C=O); $^1H$-nmr signals in the aromatic region were observed for three protons at 7.10, 6.70 (sharp and broad doublets, respectively, $J$=8 Hz), and 6.50 ppm (br s) together with the signals previously described for its side chain; hrms *m/z* 220.1458 $M^+$ (calcd for $C_{14}H_{20}O_2$, 220.1463).

A solution of 5-(2′-ketoheptan-6′-yl)-2-methylphenol (350 mg) in $Et_2O$ (50 ml) was treated with 2.2 equiv of $CH_3MgI$ and dehydrated as previously described to yield xanthorrhizol [**5a**] (260 mg, 75%). The physical and spectroscopic constants of the product were the same as those reported earlier (12).

ISOPEREZONE [**6b**].—A solution of 1 g of **3a** in 20 ml of $Me_2CO$ was treated with 1 ml of $Me_2SO_4$ and 2 g of $K_2CO_3$ and heated at 40° for 1 h. The solution was filtered, concentrated, redissolved in EtOAc, washed with $H_2O$, and evaporated to yield 1 g of **3b** as a colorless oil; ir 1700 (C=O ketone), 1680 (C=O, aldehyde), 1250 $cm^{-1}$ (aromatic ether); $^1H$ nmr 9.93 (1H, s, CHO), 7.40 and 6.80 (1H each, s, ArH), 3.99 (3H, s, $OCH_3$), 3.71 (1H, m, $J$=7 Hz, CH), 2.33 (2H, br s, 11-$CH_2$), 1.20 ppm (3H, d, $J$=7 Hz, $CH_3CH$); hrms *m/z* 262.1583 $M^+$ (calcd for $C_{16}H_{22}O_3$, 262.1569).

The methoxyaldehyde **3b** (500 mg) dissolved in 2 ml of a solution obtained by mixing 1 ml of 32% $H_2O_2$ with 1 ml of *t*-BuOH was warmed at 50-60° with a catalytic quantity of $SeO_2$ (23) during 1 h. The addition of 10 ml of $H_2O$ permitted ethereal extraction of the reaction product. The organic layers were evaporated and chromatographed over Si gel, eluting with $CHCl_3$, to give 300 mg of methoxyphenol **4b** and 180 mg of the correspondent formate. The compound **4b** gave absorptions in the ir at 3400 (OH) and 1700 $cm^{-1}$ (C=O ketone); $^1H$ nmr 7.34 (1H, br s, $D_2O$ exchange), 6.41 (2H, s, ArH), 3.75 (3H, s, $CH_3O$), 2.86 (1H, m, $J$=7 Hz, CH), 2.30 (2H, br s, 11-$CH_2$), 2.03 (6H, s, $ArCH_3$, 13-$CH_3$), 1.46 (4H, m, -$CH_2CH_2$-), 1.16 ppm (3H, d, $J$=7 Hz, $CH_3$-CH); hrms *m/z* 250.1591 $M^+$ (calcd for $C_{15}H_{22}O_3$, 250.1569). The formate gave ir absorptions at 1760 and 1700 $cm^{-1}$ (C=O formate and ketone); $^1H$ nmr 8.28 (1H, sharp s, $D_2O$ no exchange), 7.66 and 7.00 (1H each, s, ArH), 3.83 (3H, s, $CH_3O$), and the signals previously described for its side chain.

The formate in EtOH (10 ml) was treated with 10% $K_2CO_3$ at 50° for 15 min and neutralized (10% HCl). Extraction with $Et_2O$ yielded the methoxyphenol **4b**.

The compound **4b** (400 mg) in $Et_2O$ was treated with 2.2 equiv of $CH_3MgI$ and dehydrated (catalytic $I_2$). Work-up as described above yielded curcuhydroquinone 4-methyl ether [**5c**] (375 mg, 94%); ir 3450 $cm^{-1}$ (OH), $^1H$ nmr 6.31 (1H, s, OH, $D_2O$ exchange), 5.01 (1H, m, CH=), 3.71 (3H, s, MeO), 2.80 (1H, m, $J$=7 Hz, CH), 2.07 (3H, s, $ArCH_3$), 1.63 and 1.46 (2×3 H br singlets, C=C $(CH_3)_2$), 1.10 (3H, d, $J$=7 Hz, $CH_3CH$-); hrms *m/z* 248.1752 $M^+$ (calcd for $C_{16}H_{24}O_2$, 248.1776).

A solution containing 375 mg (1.6 mmol) of curcuhydroquinone 4-methyl ether [**5c**] in MeCN (15 ml) was reacted with catalytic quantities of $Cu_2Cl_2$ and Cu° powder (10 mg each) (24,25). The reaction was

stirred at room temperature in an $O_2$ atmosphere for 4 h. It was then acidified with 10% HCl and extracted three times with $Et_2O$ (30 ml). The combined extracts were dried and concentrated to give a yellow oil [**5d**] (350 mg, 87%) that was used without purification. Demethylation (26) of **5d** was carried out with AgO (380 mg, 3 mmol) in $Me_2CO$ (15 ml) and 6N $HNO_3$ (0.7 ml). The reaction was kept at 50° during 10-15 min (until AgO was consumed) and then quenched by addition of 10 ml of $H_2O$ and 10 ml of $CHCl_3$. The aqueous phase was extracted three times with $CHCl_3$. The organic layers were combined, dried over $MgSO_4$, and concentrated to give 270 mg (82%) of isoperezone [**6b**], yellow plates, mp 97-98°; ir 3250 (OH) and 1670 $cm^{-1}$ (quinoid ring); $^1H$ nmr similar to perezone [**6c**] except the signals corresponding to the quinoid proton (1H, s, 5.46) and the quinoid Me (3H, s, 2.06 ppm). Acetylation of **6b** with $Ac_2O$-NaOAc by the conventional method gave 2-acetoxy-5-desoxyperezone (isoperezone acetate) (9).

PEREZONE [**6c**].—To a solution of aldehyde **3a** (500 mg) in MeCN under an $O_2$ atmosphere was added catalytic $Cu_2Cl_2$ and Cu° powder (15 mg each). After 12 h the product was worked up as described above, yielding 2-(2′-ketoheptan-6′-yl)-3,4-dihydroxy-5-methylbenzaldehyde (480 mg, 90%); ir 3450 (OH), 1680, 1710 $cm^{-1}$ (C=O); $^1H$ nmr 9.98 (1H, s, CHO), 8.48 (2H, br s, $D_2O$ exchange), 7.51 (1H, s, ArH) besides the typical signals of its side chain; hrms *m/z* 264.1379 $M^+$ (calcd for $C_{15}H_{20}O_4$, 264.1361).

A solution of 2-(2′-ketoheptan-6′-yl)-3,4-dihydroxy-5-methylbenzaldehyde (400 mg) with 5 ml of a mixture of 3% $H_2O_2$ and 1N NaOH (1:1) was stirred at 40° for 18 h in the dark. The reaction mixture was worked up as described above. The corresponding phenol (hydroxyhydroquinone) was readily oxidized but was shown not to contain an aldehyde group (ir, $^1H$ nmr). It was dissolved in anhydrous $Et_2O$ and was treated with 5 equiv of $CH_3MgI$. Work-up by the procedure described above gave an oily material which with air or Jones reagent gave yellow plates, mp 98°, characterized as perezone [**6c**] (8) (73%).

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