Journal of Natural Products
Vol. 48, No. 6, pp. 948-951, Nov-Dec 1985

ANTITUMOR AGENTS, 75.[1] SYNTHESIS OF CYTOTOXIC ANTHRAQUINONES DIGIFERRUGINOL AND MORINDAPARVIN-B

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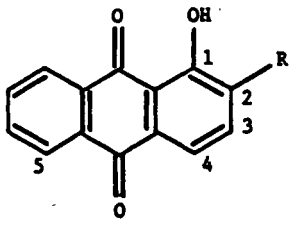
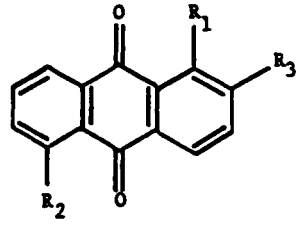
ABSTRACT.—A simple and efficient synthesis of digiferruginol (**4**) and morindaparvin-B (**10**) is described. Marschalk reaction of 1-hydroxyanthraquinone afforded 1-hydroxy-2-methylanthraquinone (**2**). Treatment of **2** with *N*-bromosuccinimide and benzoyl peroxide led to 1-hydroxy-2-bromomethylanthraquinone (**3**), which was converted to **4** with $AgNO_3$ in quantitative yield. Methylation of 1,5-dihydroxyanthraquinone yielded a dimethyl ether (**6**), which was partially demethylated with boron trifluoride to a difluoroboron chelate (**7**). Treatment of **7** with alkaline HCHO and sodium dithionate gave rise to 1-hydroxy-2-hydroxymethyl-5-methoxyanthraquinone (**9**). Cleavage of the 5-methyl ether of **9** with boron tribromide furnished **10**.

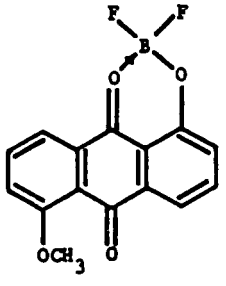
We reported recently on the isolation of a number of cytotoxic antileukemic anthraquinones from *Morinda parvifolia* (1,2). Among these anthraquinones, the new morindaparvin-B (**10**) and the known digiferruginol (**4**), which differs from **10** by lacking a 5-hydroxy group, were isolated in minute quantity and showed significant cytotoxicity. For example, compound **4** demonstrated an ED_{50}=0.09 μg/ml against the in vitro growth of KB tissue culture cells. It is important to produce **4** and **10** in quantity by synthesis, as this will not only establish the structure of **10** but also enable a detailed evaluation of their in vivo antitumor activity. Previously, aloe-emodin (**11**), a



1 R=H
2 R=CH_3
3 R=CH_2Br
4 R=CH_2OH



5 R_1=R_2=OH, R_3=H
6 R_1=R_2=OCH_3, R_3=H
8 R_1=OH, R_2=OCH_3, R_3=H
9 R_1=OH, R_2=OCH_3, R_3=CH_2OH
10 R_1=R_2=OH, R_3=CH_2OH



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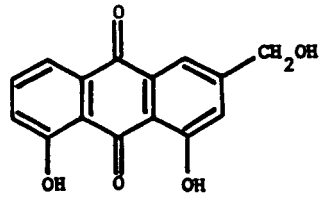

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[1]For part 74, see M. Okano, N. Fukamiya, T. Aratani, M. Juichi, and K.H. Lee, *J. Nat. Prod.*, in press.

structural analog of **10**, was reported to have in vivo antileukemic activity (3). We report herein the simple and efficient syntheses of **4** and **10**.

RESULTS AND DISCUSSION

In the synthesis of **4**, the Marschalk reaction (4), which involved a direct alkylation of 1-hydroxyanthraquinone (**1**) by means of HCHO and sodium dithionate in a basic solution, was employed for the synthesis of 1-hydroxy-2-methyl-anthraquinone (**2**) in 42% yield. Compound **2** was synthesized previously by either Friedel-Crafts reaction via condensation of phthalic anhydride and *o*-cresol in less than 10% yield (5,6), or by condensation of 3-(phenylsulfonyl)-1 (3*H*)-isobenzofuranone and 6-methyl-2-cyclohexen-1-one with lithium *tert*-butoxide in THF to yield a 9,10-dihydroxy-1,2,3,4-tetrahydroanthracen-2-methyl-1-one followed by treatment with *N*-bromosuccinimide in Me_2CO/H_2O and triethylamine (7). Treatment of **2** with *N*-bromosuccinimide and a catalytic amount of benzoyl peroxide afforded 1-hydroxy-2-bromomethylanthraquinone (**3**) in 70% yield. Subsequent treatment of **3** with $AgNO_3$ resulted in the formation of 1-hydroxy-2-hydroxymethylanthraquinone, i.e., digiferruginol (**4**), in quantitative yield.

The synthesis of **10** started with the methylation of 1,5-dihydroxyanthraquinone (**5**) to the corresponding dimethyl ether (**6**) by methyl *p*-toluenesulfonate in 67% yield. Partial demethylation of **6** with boron trifluoride according to Preston (8) afforded 84% yield of the difluoroboron chelate (**7**). Structural proof of **7** was accomplished by either heating **7** with MeOH or treatment of **6** with H_2SO_4 to yield the known 1-hydroxy-5-methoxyanthraquinone (**8**). Conversion of **7** to 1-hydroxy-2-hydroxymethyl-5-methoxyanthraquinone (**9**) by aldol condensation with alkaline HCHO and sodium dithionate was achieved in 87% yield. Subsequent cleavage of the 5-methyl ether of **9** with boron tribromide gave rise to 1,5-dihydroxy-2-hydroxymethylanthraquinone, i.e., morindaparvin-B (**10**), in 50% yield (a 30% overall yield from **5**).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Ir spectra were recorded on a Perkin-Elmer 257 grating ir spectrometer. ^{1}H-nmr spectra were determined in $CDCl_3$ with a JEOL JNM-FX 60 NMR Spectrometer using TMS as an internal standard. Silica gel (Merck silica gel 70-230 mesh) was used for column chromatography, and precoated silica gel (Analtech silica gel GF 0.25 mm or 1mm) was used for tlc. Detection of components was with a uv lamp. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee.

1-HYDROXY-2-METHYLANTHRAQUINONE (**2**).—A mixture of 1-hydroxyanthraquinone (**1**) (10 g, 44.6 mmol) and sodium dithionate (20 g, 115 mmol) in 1.5% aqueous NaOH (1 liter) was allowed to stand under N_2 for 30 min and warmed to 50°. To the above mixture, a solution of 37% HCHO (20 ml, 244 mmol) diluted with H_2O (60 ml) was added slowly. The mixture was heated to 90° for 1 h, bubbled with air for 16 h, then acidified with concentrated HCl and heated for 1 h on a steam bath. After cooling, the yellowish-green precipitate (6 g) was collected and purified by column chromatography on silica gel with C_6H_6-$CHCl_3$ (1:1) as eluent to yield pure **2** (4.5 g, 42%); mp 182-183° [lit. (7) mp 183-183°]; nmr δ 2.35 (s, 3H, CH_3), 7.35-8.42 (m, 6H, aromatic), and 12.91 (s, 1H, OH).

1-HYDROXY-2-BROMOMETHYLANTHRAQUINONE (**3**).—A mixture of **2** (2g, 8.4 mmol), *N*-bromosuccinimide (1.55 g, 8.7 mmol) and benzoyl peroxide (130 mg) in CCl_4 (230 ml) was refluxed for 1 h under a nitrogen atmosphere and worked up as usual. The crude product was crystallized from $CHCl_3$ to give **3** (1.9 g, 70%) as orange needles; mp 194-196° [lit (10) mp 190-191°]; nmr δ 4.63 (s, 2H, CH_2Br), 7.60-8.95 (m, 6H, aromatic), and 13.16 (s, 1H, OH).

DIGIFERRUGINOL (**4**).—To an EtOAc-Me_2CO (1:1) solution (50 ml) of **3** (1 g, 3.2 mmol) was added 2% aqueous $AgNO_3$ (50 ml). This bi-layer mixture was stirred in the dark at room temperature for 24 h. The organic layer was washed with brine followed by the usual workup and recrystallization form $CHCl_3$ to give orange-yellow crystals of **4** (801 mg) in quantitative yield; mp 212-213° [lit (6) mp 212-214°]; ^{1}H nmr δ 2.34 (t, 1H, OH), 4.87 (d, 2H, CH_2OH), 7.83 (m, 4H, aromatic), 8.30 (m, 2H, H-5 and H-8),

and 13.04 (s, 1H, OH); the ir and nmr spectra of this product were identical with those of naturally occurring digiferruginol.

1,5-DIMETHOXYANTHRAQUINONE (**6**).—A mixture of anthraquinone **5** (20 g, 83.3 mmol), anhydrous K_2CO_3 (80 g), *o*-dichlorobenzene (600 ml), and methyl *p*-toluenesulfonate (100 g, 536 mmol) was stirred under reflux for 3 h followed by filtration. The orange-yellow crystals (**6**) (15 g, 67%), formed in the filtrate upon cooling, were collected; mp 233-236°, sufficiently pure for the next reaction. A sample of **6** was purified by ptlc [C_6H_6-$CHCl_3$ (1:9), Rf=0.16]; mp 237-239° [lit (11) mp 236°]; nmr δ 4.04 (s, 6H, OCH_3) and 7.10-8.60 (m, 6H, aromatic).

DIFLUOROBORON CHELATE OF 1-HYDROXY-5-METHOXYANTHRAQUINONE (**7**).—To a solution of **6** (12 g, 44.8 mmol) in *o*-dichlorobenzene (500 ml) was added boron trifluoride etherate (7.3 g, 51.2 mmol) with stirring. The reaction mixture was heated under reflux for 30 min, then allowed to cool. The resulting crystals were collected and washed with hexane to give **7** (12 g, 84%), as dark brown crystals; mp 263-266°; ^{1}H nmr δ 4.11 (s, 3H, OMe) and 7.25-8.32 (m, 6H, aromatic); ir (KBr) 3450, 1674, 1612, 1462, 1265, and 1062 cm^{-1}.

1-HYDROXY-5-METHOXYANTHRAQUINONE (**8**).—*Method A*.—A solution of **6** (1.0 g, 3.7 mmol) in H_2SO_4 (96%, 30 ml) was heated to 100° for 3 h. The reaction mixture was cooled and added slowly to ice H_2O (2 liters) with stirring. The usual work-up followed by chromatography on silica gel [C_6H_6-$CHCl_3$ (1:10)] and crystallization from $CHCl_3$/EtOH gave **8** (0.57 g, 60%), as yellow needles; mp 182.5-183.5° [lit (11) mp 163-164°]; ^{1}H nmr δ 4.06 (s, 3H, OMe), 7.10-8.10 (m, 6H, aromatic), and 12.46 (s, 1H, OH).

Method B.—The chelate **7** (1 g, 3.3 mmol) was dissolved in MeOH (50 ml) and heated to 50-60° for 10 min. The product was crystallized from $CHCl_3$/EtOH to yield **8** (0.72 g, 85%). *Anal.* calcd. for $C_{15}H_{10}O_4$: *m/z* 254.0579 (M+). Found: *m/z* 254.0577.

1-HYDROXY-2-HYDROXYMETHYL-5-METHOXYANTHRAQUINONE (**9**).—To a solution of difluoroboron chelate (**7**, 8.3 g, 27.5 mmol) in 0.1 N NaOH (4.2 liters) under N_2 was added sodium dithionate (10 g, 57.4 mmol) followed by 37% HCHO (15 ml, 185 mmol). The reaction mixture was heated to 50° for 3 h, then acidified with concentrated HCl. The resulting precipitate was collected to give crude **9** (6.8 g, 87%), which was sufficiently pure for the next reaction. A sample of **9** purified by ptlc [EtOAc-$CHCl_3$ (1:10); Rf=0.14] yielded a yellow powder; mp 202-203°; ^{1}H nmr δ 2.43 (t, 1H, OH), 4.06 (s, 3H, Ome), 4.83 (d, 2H, CH_2OH), 7.27-8.10 (m, 5H, aromatic), and 12.85 (s, 1H, OH); ir (KBr) 3240, 1666, 1632, 1585, and 1270 cm^{-1}: *Anal.* calcd. for $C_{16}H_{12}O_5$: *m/z* 284.0683 (M+). Found: *m/z* 284.0676.

MORINDAPARVIN-B (**10**).—To a dry-ice acetone-cooled solution of methoxyanthraquinone (**9**) (2.27 g, 8 mmol) in dry CH_2Cl_2 (2 liters) was added dropwise a solution of BBr_3 (10.0 g, 40.2 mmol) in dry $CHCl_3$ (100 ml) with stirring. The reaction mixture was stirred for 2 h followed by extraction with H_2O. The usual workup followed by chromatography on silica gel [EtOAc-$CHCl_3$ (1:10)] and crystallization from $CHCl_3$-Me_2CO gave **10** (1.3 g, 60%), as orange-yellow crystals; mp 209-210°; ^{1}H nmr (250 MHz) δ 2.35 (b, 1H, OH), 4.89 (b, 2H, CH_2), 7.34 (dd, *J*=8.8 and 1.3 Hz, 1H, H-6), 7.69 (dd, *J*=8.8 and 7.5 Hz, 1H, H-7), 7.80 (d, *J*=7.90 Hz, 1H, H-3), 7.85 (dd, *J*=7.5 and 1.3 Hz, 1H, H-8), 7.87 (d, *J*=7.90 Hz, 1H, H-4), 12.68 (s, 1H, OH), and 13.07 (s, 1H, OH); ir (KBr) 3280, 1630, 1606, 1430, and 1267 cm^{-1}. *Anal.* calcd. for $C_{15}H_{10}O_5$: C, 66.67; H, 3.68. Found: C, 66.49; H, 3.72.

The tlc [silica gel, EtOAc-$CHCl_3$ (1:10)] and ir and ^{1}H-nmr spectra of this product were identical with those of naturally occurring morindaparvin-B (**10**) isolated from *M. parvifolia* (2). A mixed melting point of this product with authentic **10** also showed no depression.

ACKNOWLEDGMENTS

This investigation was supported by a grant from the National Cancer Institute (CA 17625) (KHL). We thank Dr. David Millington and Ms. Andria Dietrich of the GC-MS Facility, Department of Environmental Sciences and Engineering, School of Public Health, UNC-CH, for mass spectral data.

We thank Professor Sedat Imre, Pharmaceutical Faculty of the University of Istanbul, Turkey, for the ir and nmr spectra of digiferruginol.

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Received 29 April 1985