Journal of Natural Products
Vol. 52, No. 6, pp. 1357-1359, Nov-Dec 1989

SYNTHESIS OF MORINDAPARVIN A, AN ANTITUMOR AGENT, AND RELATED ANTHRAQUINONES

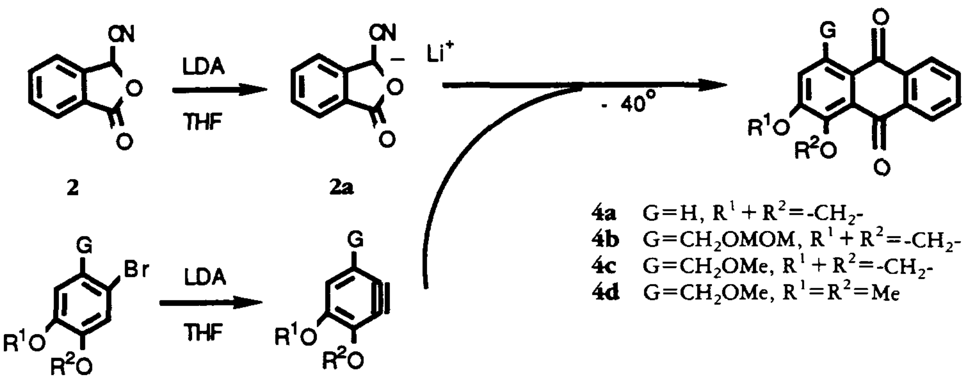
SUBHASH P. KHANAPURE and EDWARD R. BIEHL*

Department of Chemistry, Southern Methodist University, Dallas, Texas 75275

ABSTRACT.—The efficient preparation of morindaparvin A [**4a**] and several related compounds by the reaction of appropriately substituted haloarenes and 3-cyanophthalide with lithium diisopropyl amide under aryne-forming conditions is described.

In 1982, Chang *et al.* (1) reported the isolation of morindaparvin A [**4a**], a novel anthraquinone possessing relatively high biological activity, from the plant *Morinda parvifolia* Bartl. (Rubiaceae). The structure of **4a** was identified as 1,2-methylenedioxyanthraquinone by synthesis from alizarin and dibromomethane. Although these workers prepared several ester derivatives of alizarin (e.g., mono- and diacetates, cinnamates, and senecioates) and tested them for biological activity, analogues of **4a** were not synthesized and studied.

Recently, a quick and facile synthesis of anthraquinones possessing a wide variety of substitution patterns was described (2–4).[1] The method consists of treating readily accessible bromoarenes and 3-cyanophthalides with lithium diisopropylamide (LDA) under aryne-forming conditions. We report herein the extension of this method to the preparation of morindaparvin-A [**4a**] and several novel related compounds **4b**–**4d**. As shown in Scheme 1, the synthesis involves treating unsymmetrical arynes **3a**–**3d** generated from bromoarenes **1a**–**1d**, respectively, and LDA with the pre-formed lithium carbanion **2a** of 3-cyanophthalide [**2**]. Subsequent demethylation of the MOM-protected derivative **4b** by acidic hydrolysis (48% HBr) gave 4-(hydroxymethyl)morindaparvin A [**5**]. The introduction of the hydroxymethyl group is particularly significant because this group is known to enhance the biological activity of certain anthraquinones (1,5,6).



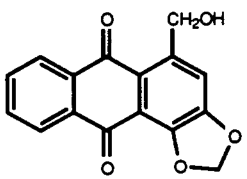
4a G=H, R^1+R^2=-CH_2-
4b G=CH_2OMOM, R^1+R^2=-CH_2-
4c G=CH_2OMe, R^1+R^2=-CH_2-
4d G=CH_2OMe, R^1=R^2=Me

1a G=H, R^1+R^2=-CH_2-
1b G=CH_2OMOM, R^1+R^2=-CH_2-
1c G=CH_2OMe, R^1+R^2=-CH_2-
1d G=CH_2OMe, R^1=R^2=Me

3a G=H, R^1+R^2=-CH_2-
3b G=CH_2OMOM, R^1+R^2=-CH_2-
3c G=CH_2OMe, R^1+R^2=-CH_2-
3d G=CH_2OMe, R^1=R^2=Me

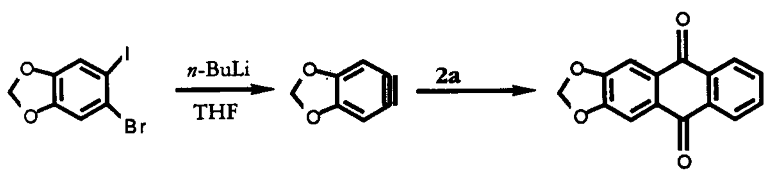
SCHEME 1

[1]Additional results from our laboratory have been submitted for publication.



5

Furthermore, the isomeric analogue of morindaparvin A, 2,3-methylenedioxy-anthraquinone [8] was prepared (65% yield) in similar fashion from cyanophthalide **2a** and 4-bromo-5-iodo-1,2-methylenedioxybenzyne [6] with the exception that the symmetrical aryne 4,5-methylenedioxybenzene [7] was generated by the action of *n*-butyllithium on arene **6** (7) (Scheme 2).



6 7 8

SCHEME 2

The ^{1}H-nmr and ir spectra of **4a** were identical to those reported for morindaparvin A (1). Furthermore, the structures of the novel 4-derivatives of **4a** were consistent with their ^{1}H-nmr, ir, and ms spectra. For example, they all possessed a low-field two-proton singlet in the range of δ 5.94–6.34 (characteristic of a methylenedioxy group) and a one-proton singlet at δ 6.89, which is expected for a penta-substituted aromatic ring. The structure **5** was confirmed by its mass spectrum, which showed a molecular ion peak at *m/z* 282, and was further substantiated by the presence of an alcohol stretching band at 3375 cm^{-1} peak in its ir spectrum. The ^{1}H-nmr spectrum of **8** revealed the expected two-proton singlet at δ 6.17, and its decoupled ^{13}C-nmr spectrum exhibited eight signals, as required by the symmetry in the molecule.

In summary, this paper describes a short, efficient synthesis of the anticancer agent morindaparvin A [**4a**], the 2,3-methylenedioxy isomer **8**, and the 4-hydroxymethyl derivative **5** of **4a**.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—^{1}H-nmr spectra were measured in $CDCl_3$ solution on a WP 200-SY Bruker spectrometer. All chemical shifts are reported in ppm downfield from internal TMS. Ir spectra were recorded on a Perkin-Elmer 283 grating spectrophotometer. Mass spectra were recorded on a Hewlett-Packard Model 5988A chromatograph/mass spectrometer at 70 eV; data reported are *m/z* values for the most abundant peaks. E. Merck Si gel 9385 (230–400) was used for flash cc. All reactions were carried out in a flame-dried flask under N_2 atmosphere.

STARTING MATERIALS.—*n*-Butyllithium and haloarene **1a** were purchased from Aldrich Chemical Company. 3-Cyanophthalide and haloarenes **1c** and **1d** were available from our earlier studies (4,8). Haloarene **1b** was obtained in nearly quantitative yield by treating 2-bromopiperonyl alcohol with NaH in THF followed by (chloromethyl)methyl ether (bp 145–150°/0.25 torr): ^{1}H nmr ($CDCl_3$) δ 3.43 (s, 3H, CH_2OCH_3), 4.57 (s, 2H, $ArCH_2O$), 4.74 (s, 2H, OCH_2O), 5.97 (s, 2H, methylenedioxy), 6.97 (s, 1H, Ar-H), 7.00 (s, 1H, Ar-H).

GENERAL PROCEDURE FOR THE REACTION OF HALOARENES WITH CYANOPHTHALIDE.—In a flame-dried flask flushed with N_2, LDA (15 mmol) was prepared by adding diisopropylamine (18 mmol) into a −78° solution of *n*-BuLi (15 mmol, 2.5 M in hexane) in THF (25 ml) under an N_2 atmosphere (using septum cap technique). After the solution was stirred for 10 min at −78°, the cyanophthalide (5 mmol) in THF (25 ml) was added dropwise over 20 min. After the reaction mixture was stirred at −78° for an extra 10 min and allowed to warm to −40°, a solution of the appropriate haloarene (5 mmol) in THF (25 ml) was added dropwise over 20 min at −40°. The reaction mixture was then allowed to warm to room temperature over a period of 2 h with stirring. The resulting dark reddish solution was quenched with saturated aqueous NH_4Cl solution, the THF was evaporated under reduced pressure, and the residue was extracted with CH_2Cl_2 (3 × 50 ml). The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated (rotary evaporator) to provide crude product. Purification of the products was accomplished by flash cc using hexane-EtOAc (9:1 or 4:1, depending on the polarity of the product) as the eluent.

MORINDAPARVIN A [**4a**].—Yellow solid (from EtOAc): mp 257°, dec [lit. (1) mp 257°]; yield 65%; ^1H nmr ($CDCl_3$) δ 6.34 (s, 2H, O-CH_2-O), 7.16 (d, *J* = 8.2 Hz, 1H, H-3), 7.78–7.82 (m, 2H, H-7 and H-8), 8.0 (d, *J* = 8.1 Hz, 1H, H-4), 8.3–9.34 (m, 2H, H-6 and H-8); ir ($CHCl_3$) ν max 1675, 1590 cm^{-1}; ms *m/z* $[M]^+$ 252).

1,2-METHYLENEDIOXY-4-(METHOXYMETHOXYMETHYL)ANTHRA-5,10-QUINONE [**4b**].—Yellow solid (from EtOAc): mp 186–189°; yield 35%; ^1H nmr ($CDCl_3$) δ 4.13 (s, 3H, -OCH_2-O*Me*), 4.15 (s, 2H, Ar-CH_2-O-CH_2), 5.54 (s, 2H, Ar-CH_2-O-CH_2-OMe), 5.89 (s, 2H, methylenedioxy), 7.02 (s, 1H, H-3), 8.33–8.48 (m, 2H, H-7 and H-8), 8.91–8.95 (m, 2H, H-6 and H-8); ir ($CHCl_3$) ν max 1675, 1595 cm^{-1}; ^{13}C nmr ($CDCl_3$) δ 55.6, 68.4, 96.4, 103.6, 111.1, 117.5, 122.9, 126.5, 127.2, 132.1, 133.3, 134.0, 134.4, 141.2, 147.3, 153.7, 182.2, 183.0; hrms calcd for $C_{18}H_{14}O_6$, 326.0786, found 326.0786.

1,2-METHYLENEDIOXY-4-(METHOXYMETHYL)ANTHRA-5,10-QUINONE [**4c**].—Yellow needles (from C_6H_6): mp 210–215°; yield 55%; ^1H nmr ($CDCl_3$) δ 3.2 (s, 3H, OMe), 4.58 (s, 2H, CH_2-OMe), 5.94 (s, 2H, O-CH_2-O), 6.89 (s, 1H, H-3), 7.36–7.41 (m, 2H, H-6 and H-7), 7.84–8.04 (m, 2H, H-6 and H-8); ir ($CHCl_3$) ν max 1660, 1595, 1465, 1300 cm^{-1}; hrms calcd for $C_{17}H_{12}O_5$, 296.0681, found 296.0698.

1,2-DIMETHOXY-4-(METHOXYMETHYL)ANTHRA-5,10-QUINONE [**4d**].—Yellow solid (from EtOH): mp 131–132°; yield 58%; ^1H nmr ($CDCl_3$) δ 3.58 (s, 3H, CH_2-OMe), 3.99 (s, 3H, OMe), 4.02 (s, 3H, OMe), 5.03 (s, 2H, CH_2-OMe), 7.69–7.73 (m, 3H, H-3, H-7 and H-8), 8.11–8.19 (m, 2H, H-6 and H-9); ir ν max ($CHCl_3$) 1660, 1595, cm^{-1}; hrms calcd for $C_{18}H_{16}O_5$, 312.0993, found 312.1009.

1,2-METHYLENEDIOXY-4-(HYDROXYMETHYL)ANTHRA-5,10-QUINONE [**5**].—To a solution of **4d** (200 mg) in THF (10 ml) was added 48% HBr (5 ml). The mixture was stirred at room temperature for 30 min. THF was removed under reduced pressure, and the aqueous acidic layer was extracted with CH_2Cl_2 (2 × 25 ml). The combined extracts were washed with H_2O followed by brine and dried ($NaSO_4$). The usual workup followed by purification by flash cc over Si gel using EtOAc as an eluent gave the pure product **8** (160 mg) in 92% yield as a yellow solid (from EtOAc): mp 171–173°; ^1H nmr ($CDCl_3$) δ 4.93 (s, 2H, CH_2-OH), 6.33 (s, 2H, methylenedioxy), 6.34 (s, 1H, OH), 7.31 (s, 1H, C_3 Ar-H), 7.77–7.82 (m, 2H, H-7 and H-8), 7.82–8.30 (m, 2H, H-6 and H-9); ir ($CHCl_3$) ν max 3375, 1660, 1590 cm^{-1}; hrms calcd for $C_{16}H_{10}O_5$, 282.0525, found 282.0537 (found C 68.21%, H 3.62; $C_{16}H_{10}O_5$ requires C 68.08, H 3.57).

2,3-METHYLENEDIOXYANTHRA-5,10-QUINONE (ANALOGUE OF MORINDAPARVIN A) [**8**].—Yellow needles (from EtOAc), mp 225–226°; yield 65%; ^1H nmr ($CDCl_3$) δ 6.17 (s, 2H, O-CH_2-O), 7.68 (s, 2H, H-1 and H-4), 7.70–7.79 (m, 2H, H-7 and H-8), 8.24–8.29 (H-6 and H-9); ^{13}C nmr ($CDCl_3$) δ 102.6, 106.4, 127.9, 130.9, 133.4, 133.8, 152.7, 182.0; ir ($CHCl_3$) ν max 1660, 1595, 1465, 1300 cm^{-1}; hrms calcd for $C_{15}H_8O_4$, 252.0420, found 252.0411. Yellow solid (from EtOAc): mp 171–173°; found C 71.52%, H 3.16; $C_{15}H_8O_4$ requires C 71.43, H 3.20.

ACKNOWLEDGMENTS

This work was sponsored in part by Grant N-118 from the Welch Foundation, Houston, Texas and by the donors of the Petroleum Research Fund, administered by the American Chemical Society. High resolution mass spectral determinations were prepared by the Midwest Center for Mass Spectrometry, a National Science Foundation Regional Instrumentation Facility (Grant No. CHE 8211164).

LITERATURE CITED

1. P. Chang, K.H. Lee, T. Shingu, T. Hirayama, I.H. Hall, and H.C. Huang, *J. Nat. Prod.*, **45**, 206 (1982).
2. S.P. Khanapure, T.R. Reddy, and E.R. Biehl, *J. Org. Chem.*, **52**, 5685 (1987).
3. S.P. Khanapure and E.R. Biehl, Paper presented at the 194th National Meeting of the American Chemical Society, New Orleans, LA Aug. 30–Sept 4, 1987; Abstract ORGN 48.
4. S.P. Khanapure and E.R. Biehl, *Heterocycles*, **27**, 2643 (1988).
5. S.M. Kupchan and A. Karim, *Lloydia*, **39**, 223 (1976).
6. P. Chang and K.H. Lee, *J. Nat. Prod.*, **48**, 948 (1985).
7. M.E. Jung, P.Y. Lam, M.M. Mansuri, and L.M. Speltz, *J. Org. Chem.*, **50**, 1087 (1985).
8. S.P. Khanapure and E.R. Biehl, *J. Org. Chem.*, (1989) in press.

Received 30 May 1989