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Approaches to the Synthesis of Tetracyclic Quinone System Related to Anthracyclinone

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ABSTRACT

Synthesis of the tetracyclic quinone compound (10) is described. The synthetic route adopted involves: preparation of the precursor 2-(2'-methoxy carbonyl benzoyl) – 1,4-benzoquinone (7), Diels-Alder reaction of the later with cyclopentadiene, [1,5]-aroyl migration in the resulting adduct (8), and finally ring closure in (9).

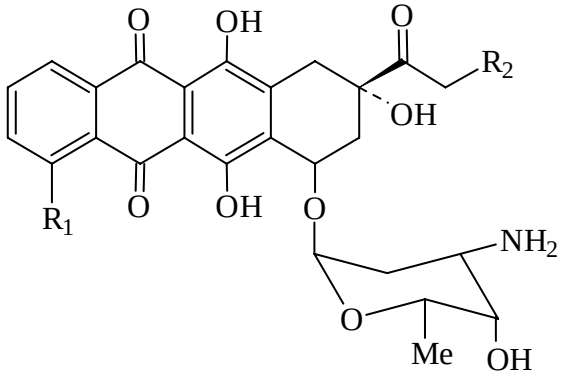
طرق لتحضير مركبات الكوينون ذات الحلقات الاربعة المتعلقة بالانثراسايكلينون

الملخص

تم تحضير مركب الكوينون (10) ذات الحلقات الاربع باعتماد مسلك تشييدي اشتمل على تحـضير المركب 2-(2'-ميثوكسي كاربونيل بنزويل)-1،4-بنزوكوينون (7) كمادة وسطية، تفاعل ديلز-ألدر بين المركب الاخير والبنتادايين الحلقي لتكوين المركب (8)، هجرة مجموعة الاروايل من نوع [5,1] لتكوين المركب (9) واخيرا غلق حلقة الكوينون للحصول على الناتج النهائي (10).

INTRODUCTION

The family of anthracycline antibiotics, of which daunorubicin (1) (Arcamone et al., 1964), doxorubicin (2) (Arcamone et al., 1969), carminomycin (3), (Brazhnikova et al., 1974), idarubicin (4) (Monneret and Florent, 1994) are important representative members, have been attracted considerable attention because of their remarkable efficacy against a wide variety of human cancers (Prieb, 1995; Rho et al., 2001).



	R_1	R_2	
1	OCH_3	H	Daunomycin
2	OCH_3	OH	Doxorubicin
3	OH	H	Carminomycin
4	H	H	Idarubicin

Synthesis of the anthracyclinones, the aglycones of anthracyclines, have been the subject of intense research in many laboratories (Kelly and Vaya, 1980; Asenjo et al., 1997; Vogel, 1998; Wulff et al., 1999). In this respect an efficient strategy towards generation of tetracyclic quinone compound, grouped under the general name anthracyclinone has been explored (Paradasani, 1982) (no experimental data available).

Based on the above strategy, synthesis of tetracyclic quinone (10) (Scheme 2) was, in part, the aim of our present work.

EXPERIMENTAL

Melting points were determined on an Electrothermal 1A 9300 Digital-Series (1998) apparatus, and are uncorrected. Infrared spectra were recorded on Perkin Elmer 257 E Nicolet 510 FT-IR Spectrophotometer (France) using NaCl film. ^{1}H-NMR spectra were recorded on Bruker Am 400 MHz (France), with TMS as internal standard, and $CDCl_3$ as solvent. Ultraviolet spectra were obtained using SP 800 PYE-Unicam UV-Vis. Spectrophotometer, in $CHCl_3$ as solvent. Thin layer chromatography (T.L.C) technique was used to monitor the reaction progress.

Methyl Hydrogen Phthalate (Eliel and Brugstahler, 1949)

Phthalic anhydride (22.2 gm, 150 mmol) and absolute methanol (15 ml) were refluxed for (2 h). The excess methanol was distilled azeotropically with dry benzene (2×12 ml) to ensure removal of unreacted methanol. The residue was diluted with benzene (90 ml). Petroleum ether (b.p. 40-60 ^{o}C) was added to the solution until the volume approximated to (180 ml) where crystallization was commenced. After standing overnight in the refrigerator, the product was collected, washed twice with (15 ml) portions of petroleum ether (b.p. 40-60 ^{o}C), and dried in air to give the product as white crystals (19.9 gm, 73.7%), m.p. 82 ^{o}C (Lit. 82-82.5 ^{o}C).

Methyl-2-chloroformylbenzoate (Eliel and Brugstahler, 1949)

A mixture of methyl hydrogen phthalate (8.0 gm, 44.4 mmol) and freshly distilled thionyl chloride (24 ml) was refluxed for (1 h) on water bath. The excess thionyl chloride was removed under reduced pressure azeotropically with benzene (3 × 2 ml) to leave a colourless liquid (11.2 ml) of the desired product. This was used immediately in the following step.

2,5-Dimethoxy-2`-methoxy carbonylbenzophenone (5) (Bentley, 1959)

To a stirred mixture of 1,4-dimethoxy benzene (5 gm, 36 mmol) and anhydrous powdered aluminum chloride (9.6 gm, 72 mmol) in dry dichloromethane (75 ml) at 0 ^{o}C, was added dropwise a solution of methyl-2-chloroformyl benzoate (8.16 gm, 41.2 mmol) in dry dichloromethane (15 ml) during the course of (1 h). The red-brown mixture was stirred at 0 ^{o}C for an additional (3 hr), then treated with aqueous hydrochloric acid (0.1 N, 40 ml), and the organic layer removed. The aqueous layer was extracted with dichloromethane (2×15 ml), and the combined organic phases were washed with saturated aqueous sodium bicarbonate (2×75 ml), water (2×75 ml), and dried (Na_2SO_4). Solvent removal under vacuum gave an orange oily residue. Trituration with cold petroleum ether (b.p. 40-60 ^{o}C) afforded a yellow solid (8.6 gm, 79%), m.p. 84-87 ^{o}C, which was shown by T.L.C. to be consisted of the required product (5).

Attempted Oxidative-Demethylation of Compound (5)

a. Using Ceric Ammonium Nitrate (CAN) (Mlochowski, 1979)

A solution of CAN (1.64 gm, 3 mmol) in water (10 ml) was added dropwise over (20 min.) to a stirred solution of (5) (0.3 gm, 1 mmol) in acetonitrile (10 ml) at room temperature. The mixture was stirred for further (30 min), diluted with water (10 ml) and extracted with dichloromethane (3×10 ml). The combined extracts were washed with water (2×10 ml) and dried (Na_2SO_4). Filtration and evaporation of the solvent under vacuum afforded a dark oily residue, which could not be solidified and characterized.

b. Using Silver (II) Oxide

To a stirred suspension of silver (II) oxide (0.5 gm, 4 mmol) and benzophenone (5) (0.3 gm, 1 mmol) in acetone (10 ml), was added nitric acid (0.5 N, 12 ml). The course of the reaction was monitored by T.L.C., which still showed after (24 hr) of continuous stirring two spots: one for the starting material and the other for the product. The reaction mixture filtered (celite) and diluted with dichloromethane (20 ml). The organic layer was separated, washed with water (2 × 10 ml) and dried ($MgSO_4$). Solvent removal under vacuum afforded a dark oily residue which was difficult to solidified and characterized.

2,5-Dihydroxy-2`-methoxycarbonylbenzophenone (6) (Pardasani, 1982)

Anhydrous aluminum chloride (1.0 gm, 7.5 mmol) was added to a stirred solution of the benzophenone (5) (0.3 gm, 1 mmol) in dry dichloromethane (7 ml), the initial red colour changed to green. The stirring was continued for (1 h), then a solution of boron tribromide (0.5 ml, 5 mmol) in dry dichloromethane (3 ml) was added dropwise. After an additional (3 h) stirring, the red-brown mixture was treated with 5% aqueous hydrochloric acid (20 ml) and extracted with chloroform (10 ml). The organic layer was separated, and the aqueous layer back extracted with chloroform (3×10 ml). The combined organic phases were washed with saturated aqueous sodium bicarbonate (50 ml), water (50 ml), and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure afforded a pale yellow solid (0.21 gm, 77%), which was shown by T.L.C. to consist of one compound, *viz*. 2,5-dihydroxy-2`-methoxycarbonyl benzophenone (6), m.p. 184-187 ^oC.

2-(2`-Methoxycarbonylbenzoyl)-1,4-benzoquinone (7)

A mixture of benzophenone (6) (1.05 gm, 3.8 mmol), activated silver(I) oxide (7.5 gm, 32.3 mmol) and anhydrous sodium sulphate (7.5 gm) in dry benzene (125 ml) was refluxed with stirring for (3 hr). The suspension was filtered (celite) and the pad washed with ether (2×25 ml). Solvent removal from the combined filtrate and washings under vacuum afforded the title compound (7) (1.0 gm, 97%) as an orange solid, m.p. 111-113 ^oC.

Endo-4a,5,8,8a-tetrahydro-5,8-methano-4a,(2`-methoxycarbonyl benzoyl)-1,4-naphthoquinone (8)

Freshly distilled cyclopentadiene (2.0 ml, 25 mmol) was added to a stirred solution of the benzoquinone (7) (0.9 gm, 3.3 mmol) in dry benzene (60 ml). The initial orange colour faded rapidly to a pale yellow. T.L.C. examination after (18 h) revealed a complete reaction. Solvent removal under vacuum afforded a yellow solid (0.94 gm)

which was purified by column chromatography on silica gel (chloroform) to give yellow crystals (0.67 gm, 60%) of the title adduct (8), m.p. 121-125 ^{o}C.

Endo-5,8-dihyhdro-5,8-methano-2-(2`-methoxycarbonyl benzoyl)-1,4-dihydroxy naphthalene (9)

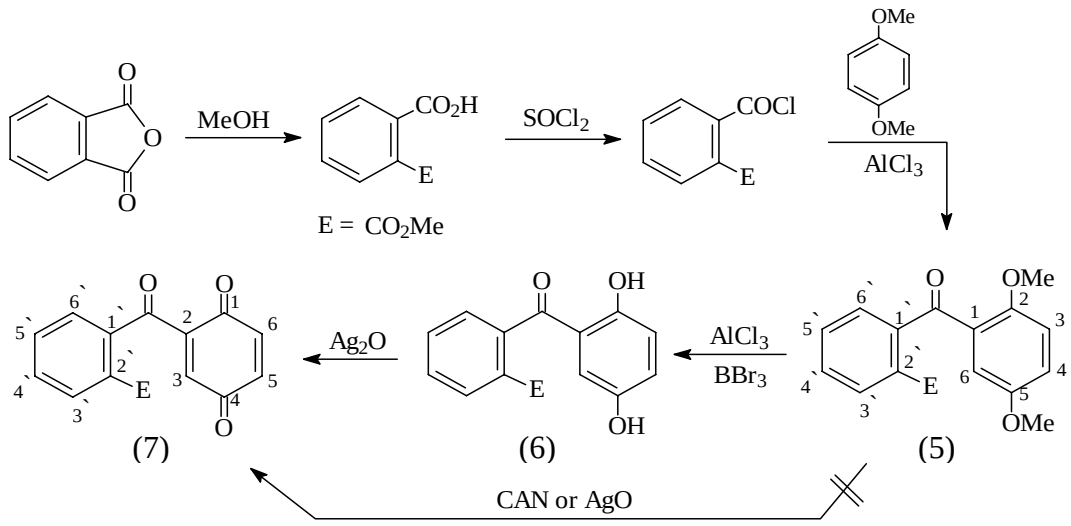
Adduct (8) (0.18 gm, 0.53 mmol) was dissolved in pyridine (2.6 ml), and stirred at 30 ^{o}C for (48 h), when T.L.C. indicated the absence of starting material. Solvent removal under vacuum afforded a dark residue which was triturated with petroleum ether (b.p. 40-60 ^{o}C) then chromatographed on silica gel (chloroform) to give a yellow solid (70 mg, 39%) of the title compound (9), m.p. 130-131 ^{o}C.

Endo-7,10-dihydro-7,10-methano-6,11-dihydroxy-5,12-naphthacenedione (10)

A solution of (9) (40 mg, 0.12 mmol) in dry dichloromethane (5 ml) was stirred with a solution of boron tribromide (0.07 ml, 0.76 mmol) in dry dichloromethane (1 ml) at 0 ^{o}C for (4 h). The dark violet solution was decomposed with cold water (7 ml), extracted with dichloromethane (4 × 5 ml), washed with water (3×5 ml) and finally dried (Na_2SO_4). Evaporation of the solvent under reduced pressure afforded a red solid (30 mg, 83%) which was shown by T.L.C. to consist of one compound. Column chromatography on silica gel (chloroform) afforded orange-red crystals of the title compound (10), m.p. 195-196 ^{o}C.

RESULTS AND DISCUSSION

Construction of the tetracyclic quinone (10) was achieved through the primarily synthesis of the substituted benzoyl benzoquinone (7) as a precursor (Scheme 1).

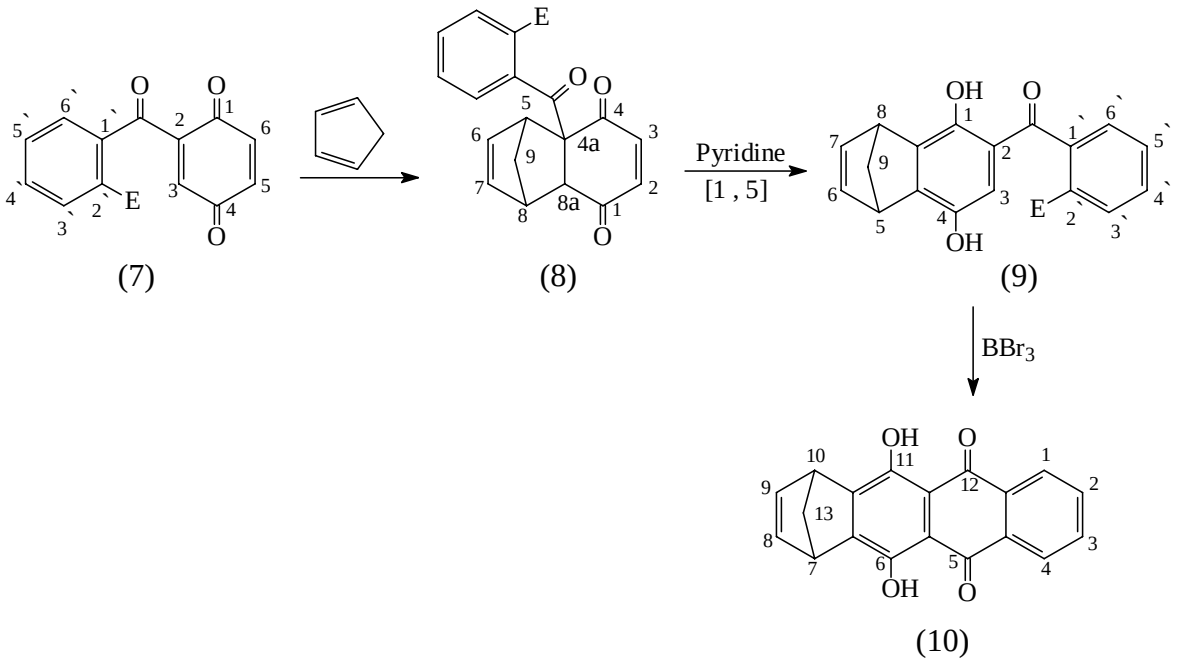


Scheme 1

Initially, Friedel-Crafts acylation of 1,4-dimethoxy benzene with freshly prepared 2-chloroformyl methyl benzoate in the presence of aluminum chloride afforded the benzophenone (5). Attempted oxidative-demethylation of the later using silver (II) oxide or CAN failed to produce the desired benzoquinone (7). However, successful demethylation of (5) was achieved by the consecutive addition of aluminum chloride and

boron tribromide which afforded the corresponding hydroquinone (6). Oxidation of (6) with silver (I) oxide gave (7) in almost quantitative yield (97%).

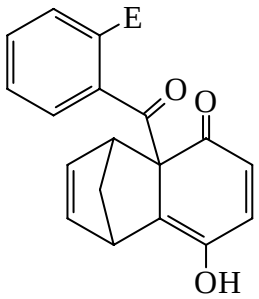
The next step in the synthetic sequence (Scheme 2) was the Diels-Alder reaction of the benzoquinone (7) with cyclopentadiene.



(7) (8) (9) (10)

Scheme 2

Subsequent [1,5]-aroyl migration in the resulting adduct (8) with pyridine afforded (9), probably via the enol intermediate (11) (Ahmed, 1984).



(11)

Finally, compound (9) underwent ring closure with boron tribromide affording (10). The spectroscopic data (Table 1) was in agreement with the expected structure.

Table 1: Spectral data of compounds (5-10).

Compd. No.	U.V. λ_{max} (nm)	I.R., ν (cm^{-1}), KBr			^{1}H-NMR δ (ppm), $CDCl_3$
		C=O	C=C	O-H	
5	258 345	1711 1647	1600	-	*
6	261 370	1698 1621	1592	3375	*
7	255	1715 1662	1575	-	3.81 (s, 3H, CO_2Me); 6.76 (d, 1H, H-5 or H-6); 6.82 (d, 1H, H-5 or H-6); 6.95 (s, 1H, H-3); 7.44 (d, 1H, H-6`); 7.59-7.69 (m, 2H, H-4`+H-5`); 8.02 (d, 1H, H-3`)
8	250	1709 1669	1614 1575	-	1.48 (d, 2H, 2H-9); 1.93 (d, 1H, H-8); 3.6 (d, 1H, H-8a); 3.77 (s, 3H, CO_2Me); 4.26 (m, 1H, H-5); 6.02 (d, 1H, H-6 or H-7); 6.21 (m, 1H, H-6 or H-7); 6.46 (d, 1H, H-2); 6.56 (d, 1H, H-3); 7.31 (d, 1H, H-6`); 7.51 (t, 1H, H-5` or H-4`); 7.67 (t, 1H, H-4` or H-5`); 7.96 (d, 1H, H-3`)
9	-	1706 1668	1614 1600	3412	*
10	252 298	1649 1637	1620 1588	3375	1.26 (m, 2H, 2H-13); 3.51 (m, 2H, H-7+H-10); 6.14 (m, 2H, H-8+H-9); 7.33 (s, 2H, H-2+H-3); 7.85 (m, 2H, H-1+H-4); 8.36 (m, 2H, OH-6+OH-11)

* ^{1}H-nmr instrument is out of use.

REFERENCES

Ahmed, B.A., 1984. Synthesis and reactions of aroyl-1,4-benzoquinones: Approaches to anthracyclinones. Ph.D. Thesis.

Arcamone, F.; Franceschi, G.; Oreezi, P.; Cassinelli, G.; Barbier, W. and Mondelli, R. 1964. Daunomycin I The structure of daunomycin. J. Am. Chem. Soc., Vol.86, 5334 p..

Arcamone, F.; Franceschi, G.; Penco, S. and Selva, A., 1969. Adriamycin (14-hydroxydaunomycin), a novel antitumor antibiotic. Tetrahedron Lett., 1007 p..

Asenjo, P.; Farina, F.; Martin, M.V.; Parades, M.C. and Soto, J.J., 1997. Polycyclic hydroxyquinones Part 29. Regiose Lective reactions of 8-sulphur-substituted furan-2-(5H)-one anion with naphthoquinone monoketals, Application to the synthesis of anthracyclinone precursors. Tetrahedron, Vol.53, 1822 p..

Bentley, K.W. and Robinson, R., 1959. A synthesis of α-anhydrotrimethyl-brazilone. Tetrahedron Let., Vol.2, 11 p..

Brazhnikova, M.G.; Zbarsky, V.B.; Ponomerenko, V.L. and Patapova, N.P., 1974. Physical and chemical characteristics and structure of carminomycin, a new antitumor antibiotic. J. Antiniot., Vol.27, 254 p..

Eliel, E.L. and Brugstahler, A.W., 1949. Synthesis of phalaldehyde and phthalaldehydic acid by the roseumund reduction. J. Am. Chem. Soc., Vol.71, 2251 p..

Kelly, T.R.; Vaya, J. and Ananthasubramanian, L., 1980. Efficient regiospecific synthesis of (±)-daunomycinone. J. Am. Chem. Soc., Vol.102, 5983 p..

Mlochowski, J.; Syper, L.; Kloc, K. and Szulc, Z. 1979. An improved synthesis of benzo- and naphthoquinones from hydroquinone dimethyl ethers. Synthesis, 521.

Monneret, C. and Florent, J.C. 1994. Isosaccharino and glucosaccharino-lactones as chirones for synthesis of natural compounds and analogs of relevance. Synlett, 304.

Pardasani, R.T. 1982. Ph.D. Thesis, University of Manchester, Cited in Reference: Ahmed, B.A., 1984, Ph.D. Thesis, University of Manchester, U.K.

Prieb, W., 1995. Anthracycline antibiotics. E.D.; American Chemical Society: Washington D.C.

Rho, Y.S.; Kim, W.J.; Park, S.; Yoo, D.J.; Kang, H.S. and Chung, S.R., 2001. Synthesis of new anthracycline derivatives including acetylsalicylic or plamitic acid moiety, Bull. Korean Soc., Vol.22, 6, 287 p..

Vogel, P., 1998. Combinatorial Diels-Alder approach to the synthesis of antitumer anthracyclines and analogues, Current Organic Chemistry, Vol.2, 255 p..

Wulff, W.D.; Su, J.; Tang, P.C. and Xu, Y.C., 1999. Studies toward the synthesis of menogaril: synthesis of A-ring precursors and their conversion to the tetracyclic core via the benzannulation reaction, Synthesis, Vol.3, 415 p..