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Unexpected Products in the Synthesis of Tetracyclic Anthrone Systems

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ABSTRACT

An unexpected bis-anthranol (11) was obtained in an attempt to synthesis 1,4-dimethxy anthrone (5a) as a precursor in the total synthesis of tetracyclic anthrone systems (7 and 8) related to anthracyclinones. Oxidative-demethylation of (11) to the corresponding quinone (12) gave the unexpected quinone methide (13). The structure of the latter and the other compounds were confined by spectroscopic measurements.

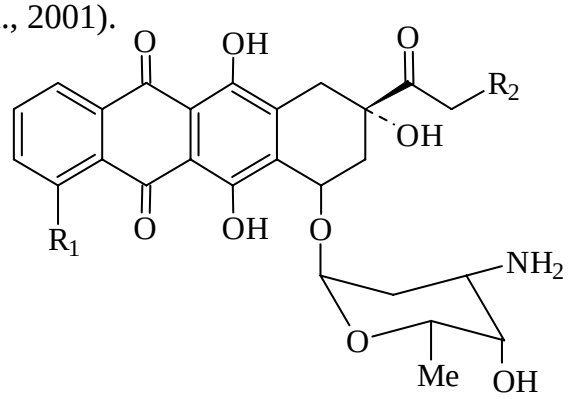
نواتج غير متوقعة في تحضير الانثرون ذات الحلقات الاربعة

الملخص

تم الحصول على المركب بس-انثرانول (11) كناتج غير متوقع عند محاولة تحضير المركب 4،1-ثنائي ميثوكسي انثرون (5a) كمادة اولية في تحضير مركبات الانثرون ذات الحلقات الاربع (7 و 8) ذات العلاقة بالانثراسايكلينون. ان سحب مجاميع المثيل واكسدة المركب (11) لم يعط الكوينون المتوقع (12)، بل اعطى الكوينون-ميثايد (13) والذي اثبت تركيبه والمركبات الاخرى بالقياسات الطيفية.

INTRODUCTION

The anthracycline antibiotics, examplified by the key functionalized types (1-4) (Arcamone et al., 1964; Arcamone et al., 1969; Brazhnikova et al., 1974; Monneret and Florent, 1994) constitute a class of natural products which is currently making a significant impact in the fields of cancer chemotherapy (Wiley, 1982; Prieb, 1995; Rho et al., 2001).

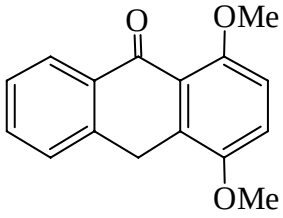


	R_1	R_2	
1	OCH_3	H	Daunomycin
2	OCH_3	OH	Doxorubicin
3	OH	H	Carminomycin
4	H	H	Idarubicin

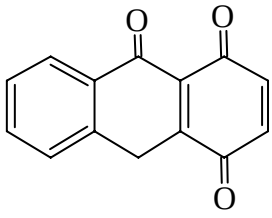
Over the years the synthesis of the anthracyclinones, the aglycones of anthracyclines, have been extensively investigated as part of the ongoing search to derive analogues with higher therapeutic index (Asenjo et al., 1997; Vogel, 1998; Wulff et al., 1999).

An excellent entry to new modification in the tetracyclic skeleton of anthracyclinone was achieved, using the well known 1,4-dimethoxy anthrone (5a) (Kim et al., 1979; Shyamasundar and Caluwe, 1981).

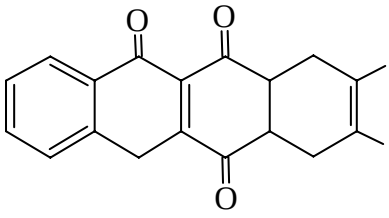
As part of our investigation in this field, we thought that the anthrone (5a) could also serve as useful precursor to the tetracyclic compounds containing anthrones (7,8). Oxidative demethylation of (5a) will give hopfully the corresponding quinone (6) on which cycloaddition reaction could be affected using different dienes to give the desired tetracyclic quinone-anthrone systems (7 and 8).



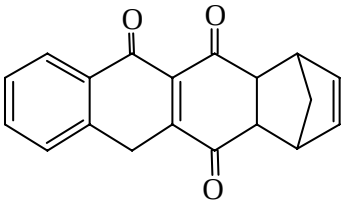
(5a)



(6)



(7)



(8)

EXPERIMENTAL

Melting points were determined on an Electrothermal 1A 9300 Digital-Series 1998 apparatus (uncorrected). Ultraviolet spectra were obtained using SP 800 PYE-Unicam UV-Vis. Spectrophotometer, in $CDCl_3$ as solvent. Infrared spectra were recorded on Perkin Elmer 590 B Spectrophotometer. ^{1}H-NMR spectra were determined (France) with Bruker Am 400 MHz, using $CDCl_3$ as solvent. Thin layer chromatography (T.L.C) technique was used to monitor the reaction progress.

Preparation of 3-bromophthalid (Hirshberg et al., 1951)

Phthalid (1.0 gm, 7.5 mmol) and N-bromo succinamide (NBS) (1.33 gm, 7.5 mmol) in dry carbone tetrachloride (20 ml) were refluxed for (30 min) under anhydrous conditions. The reaction mixture was exposed to the light of an ordinary 100 watt unforsted light bulb placed 6-8 inch from the flask. The end of the reaction indicated by the disappearance of the (NBS) from the bottom of the flask and accumulation of succinamide at the top of the reaction mixture. The succinamide is removed by filtration and the filtrate was concentrated under atmospheric pressure to 15-20 ml. Cooling of the concentrate followed by filtration gave a white solid. Crystallization from cyclohexane gave colourless crystals (1.22 gm, 75%) of 3-bromophthalid, m.p. 77-79 ^{o}C (Lit.78-80 ^{o}C).

3-(2`,5`-Dimethoxy phenyl) phthalid (9) (Kim et al., 1979)

A mixture of 3-bromophthalid (1.1 gm, 5.2 mmol) and 1,4-dimethoxybenzene (0.7 gm, 5 mmol) in dry dichloromethane (25 ml) was stirred at 0 ^{o}C for (30 min). Stannic chloride (0.63 ml, 5.5 mmol) was added dropwise *via* a syringe to the mixture and stirred for further (4 h) at 0 ^{o}C. The mixture was quenched with cold water (100 ml), transferred to a separating funnel, washed with hydrochloric acid (1 M, 2×35 ml) and then saturated aqueous sodium bicarbonate (3×15 ml). The organic layer was dried (Na_2SO_4) and evaporated till dryness to leave an oily residue which solidified upon trituration with cold ether to give a pale yellow solid (1.15 gm, 85%) of the title compound (9), m.p. 72 ^{o}C (Lit. 80 ^{o}C), (Table 1).

2-(2`,5`-Dimethoxybenzyl) benzoic acid (10)

3-(2`,5`-Dimethoxyphenyl) phthalid (9) (0.74 gm, 2.7 mmol) was treated with zinc dust (7.0 gm), copper sulphate pentahydrate (0.1 gm), and 10% aqueous sodium hydroxide (20 ml). The mixture was heated under reflux for (4 h), then cooled and filtered, and the residue was washed with water (5 ml). The combined filtrate and washings were washed with ether (3 × 10 ml) and then acidified to pH 1. The resulting white precipitate was extracted with dichloromethane (2 × 10 ml) and dried (Na_2SO_4). Evaporation of the solvent under vacuum afforded a white solid (0.49 gm, 67%) of the title compound (10), m.p. 111-113 ^{o}C, Table (1).

Attempted Synthesis of 1,4-dimethoxy-9-anthrone (5a)

A solution of (10) (0.46 gm, 1.69 mmol) in dry dichloromethane (10 ml) containing trifluoroacetic anhydride (TFAA) (0.47 ml, 3.32 mmol) was stirred at room temperature for (30 min). Evaporation of the mixture to dryness under vacuum afforded a yellowish-brown solid. Crystallization from ether afforded orange crystals, which was found to be bisanthranol (11) (0.37 gm, 86%), m.p. 169-172 ^{o}C, Table (1).

Attempted Oxidative-Demethylation of (11):

a- Using Ceric Ammonium Nitrate (CAN):

A solution of ceric ammonium nitrate (1.41 gm, 2.58 mmol) in water (5 ml) was added dropwise over (10 min.) to a stirred solution of bisanthranol (11) (0.217 gm, 0.42 mmol) in acetonitrile (5 ml) at room temperature. The mixture was stirred for further (30 min), diluted with water (5 ml) and extracted with dichloromethane (4 × 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 an orange-red solid which was found to be (13) (0.21 gm, 97%), m.p. 203-204 ^{o}C, Table (1).

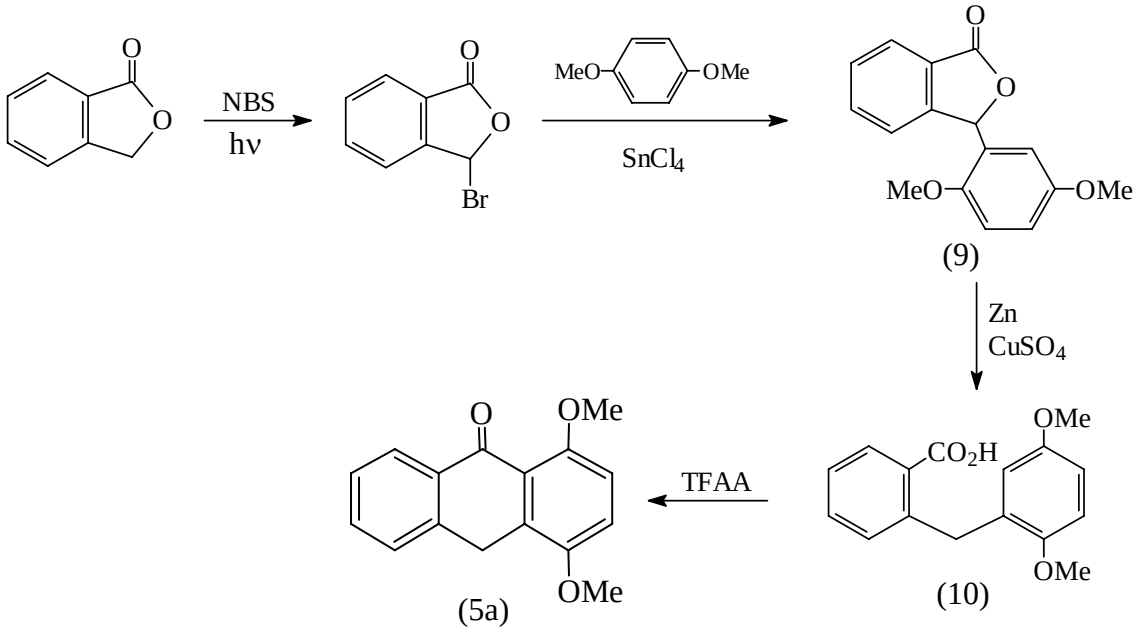
b- Using Silver (II) Oxide:

Nitric acid (0.5 N, 2.36 ml) was added to a stirred suspension of silver (II) oxide (100 gm, 0.8 mmol) and bisanthranol (11) (50 mg, 0.1 mmol) in acetone (3 ml). The solution turned orange, the course of the reaction was monitored by T.L.C. which revealed after (10 min) that all of the starting material has been consumed (by this time all silver (II) oxide was disappeared). The reaction mixture was diluted with chloroform (10ml), water (7 ml) and stirred for (5 min). The organic layer was separated, washed

with water (10 ml), and dried ($MgSO_4$). Solvent removal under vacuum afforded a red oily residue. Trituration with cold ether afforded an orange solid (40 mg). Column chromatography on silica gel (dichloromethane: petroleum ether 40-60 ^oC 1:2) afforded orange crystals (20 mg, 40%) of (13). M.p. and T.L.C. were identical with that obtained from the above experiment (a).

RESULTS AND DISCUSSION

As mentioned previously, our synthetic strategy toward the products (7,8), primarily, requires preparation of the anthrone (5a) (Scheme 1) (Kim et al., 1979).



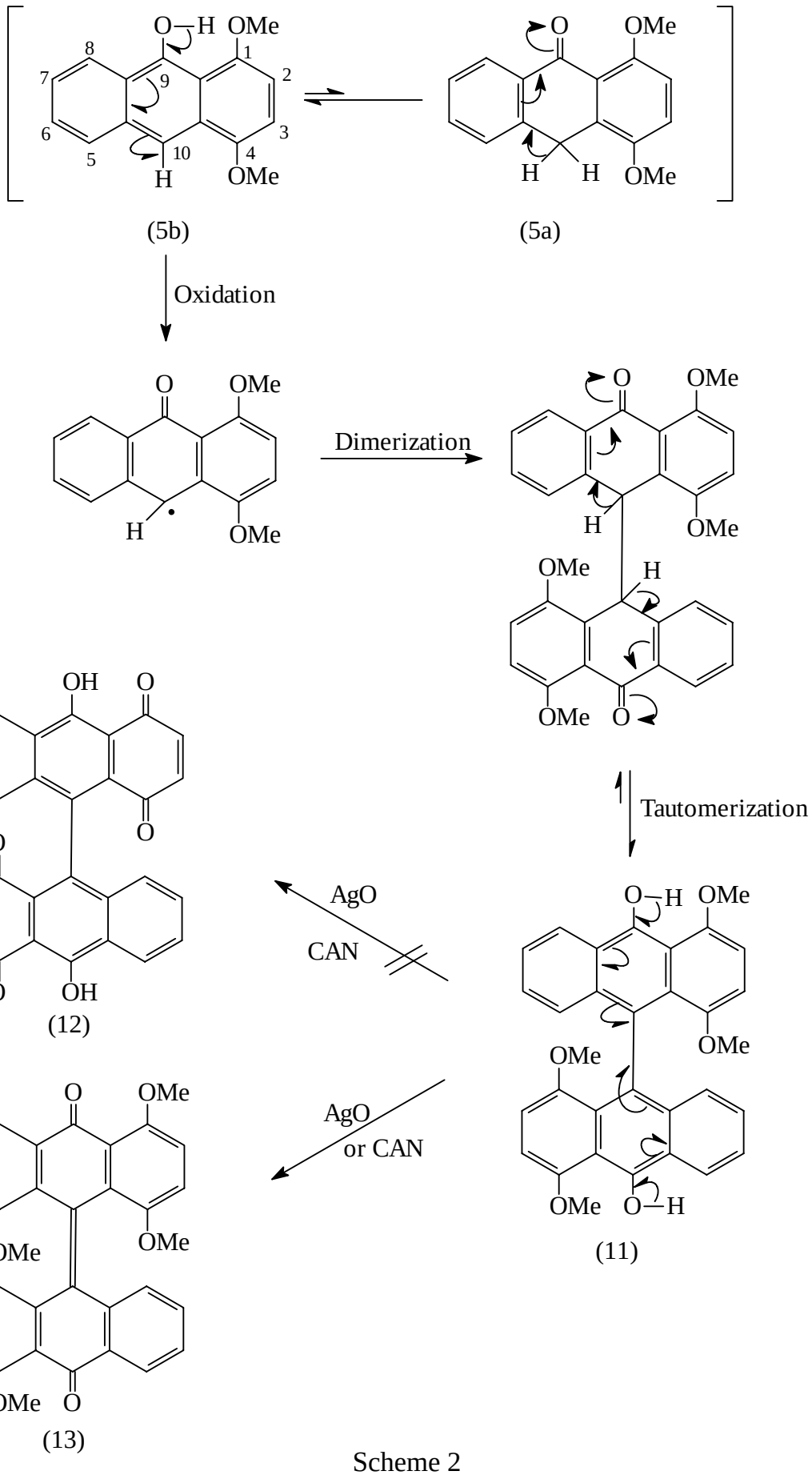
Scheme 1

Thus, condensation of 1,4-dimethoxybenzene with 3-bromophthalid afforded (9), reduction of the later with zinc dust gave (10). Ring closure in compound (10) was expected to afforde (5a) mainly in the tautomeric anthranol form (5b). Similar observation was reported in the literature (Kim et al., 1979; Shyamasundar and Caluwe, 1981). But the ^{1}H-NMR spectrum of the isolated product (Fig. 1) clearly indicate the absence of C-10 proton signal which was reported (Shyamasundar and Caluwe, 1981) to appear as a multiplet (m) coincides with the aromatic protons in 60 MHz instrument.

In view of this fact, one can speculate, that the anthranol (5b) may underwent air oxidation affording radical species, which inturn could dimerize to give bisanthrone, which was quickly tautomerized to bis-anthranol (11). This compound has no proton at C-10 (Scheme 2).

Compound (11) was treated with the oxidative-demethylating agents (Ago or CAN) hopfully to get the corresponding bisquinone (12) (Scheme 2). Instead the bisquinone methide (13) was isolated.

The identity of the separated products was established from their spectroscopic data as shown in Table (1), Fig. (1,2).


(5b)
(5a)
Oxidation
Dimerization
Tautomerization
AgO
CAN
AgO
or CAN
(12)
(11)
(13)

Scheme 2

Table 1: Spectral data of compounds (9, 10, 11 and 13).

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	
9	250 298	1762	1600	-	*
10	250 293	1685	1600	3375-3500	*
11	265 378	1621	1585	3280	3.8 (s, 6H, OMe-1+OMe-1`); 4.0 (s, 6H, OMe-4+OMe-4`); 6.45 (d, 2H, H-2+H-2` or H-3+H-3`); 6.55 (d, 2H, H-2+H-2` or H-3+H-3`); 7.4 (t, 2H, H-6+H-6` or H-7+H-7`); 7.5 (t, 2H, H-6+H-6` or H-7+H-7`); 7.65 (d, 2H, H-5+H-5` or H-8+H-8`); 8.4 (d, 2H, H-5+H-5` or H-8+H-8`); 10.7 (s, 2H, 2OH)
13	225	1670	1634 1600 1581	-	4.01 (s, 12H, OMe-1+OMe-1`+OMe-4+OMe-4`); 7.36 (s, 4H, H-2+H-2`+ H-3+H-3`); 7.70-7.73 (m, 4H, H-6+H-6`+H-7+H-7`); 8.16-8.18 (m, 4H, H-5+H-5`+H-8+H-8`)

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

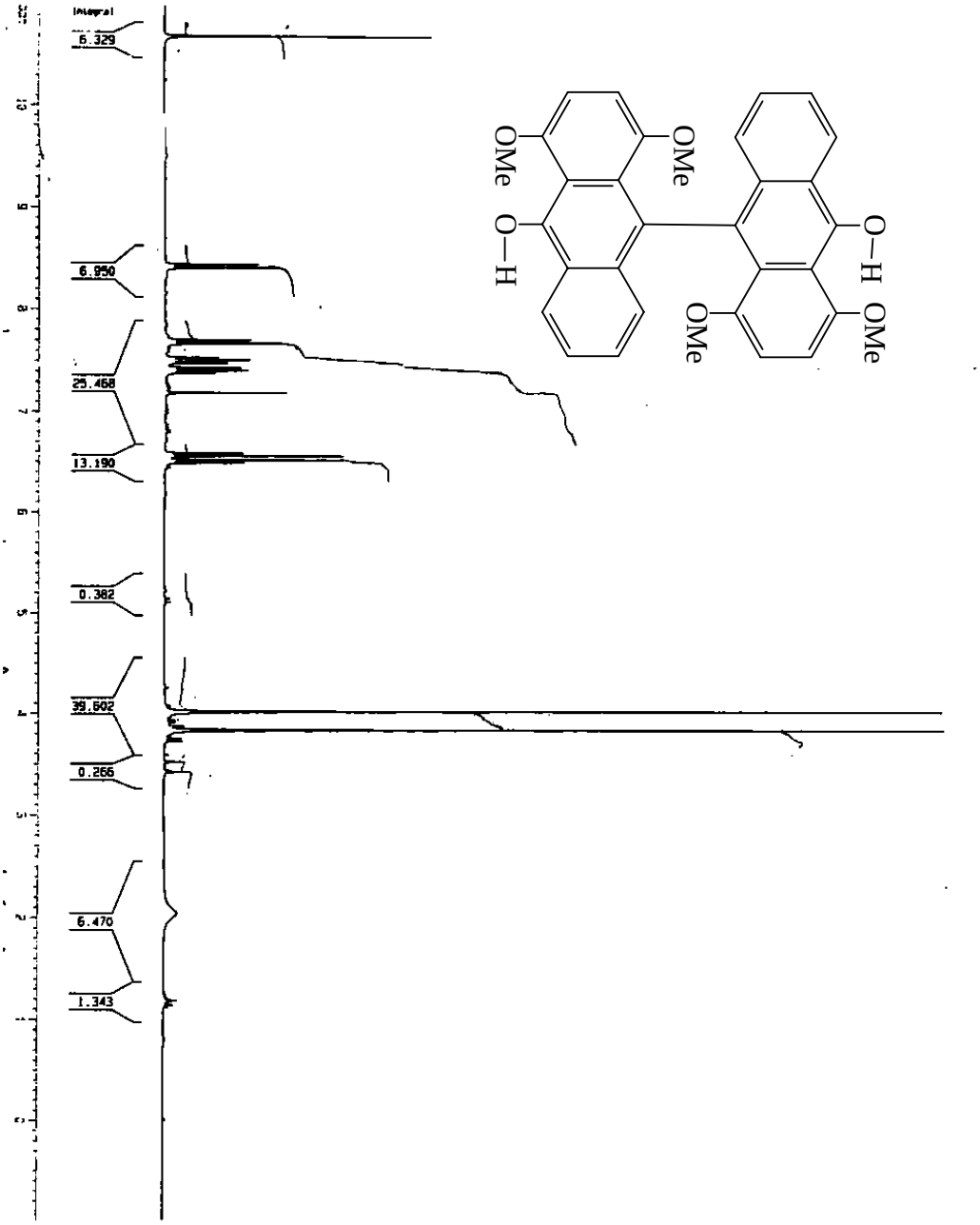


Fig. 1: ^{1}H-NMR spectrum of compound (11)

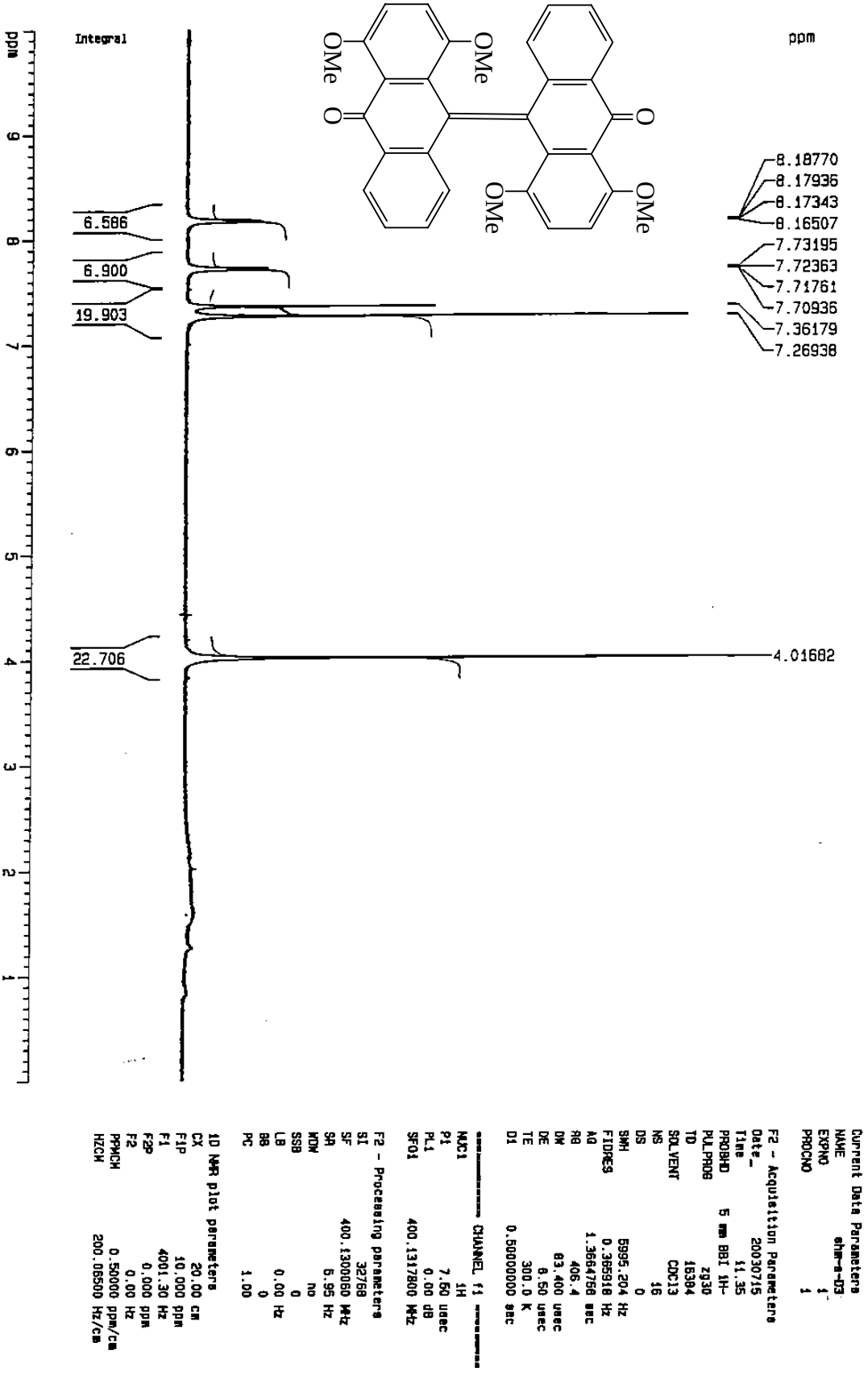


Fig. 2: ^{1}H-NMR spectrum of compound (13)

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