The Total Synthesis of β-Lapachone

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Received May 18, 1992

The synthesis of β-lapachone has been accomplished in eight steps with an overall yield of twenty-three percent starting from *alpha*-naphthol. The yields from the various steps were sufficiently good to insure that the derivatives of β-lapachone which might be effective against Chagas' disease could be obtained in reasonable amounts.

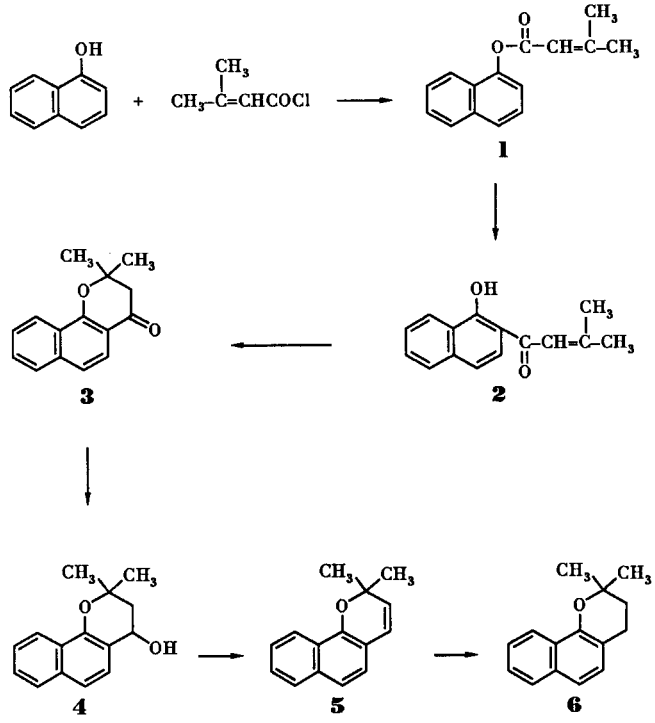
J. Heterocyclic Chem., **29**, 1457 (1992).

Introduction.

The biological activity of lapachol and β-lapachone have been well documented; for example, lapachol has been shown to protect mice from the cercaria of *Schistosoma mansoni* [1]. β-Lapachone has activity *in vitro* against Chagas' disease, an incurable infection which causes early death of about eighteen million South Americans. Unfortunately the *in vivo* activity is lost; however, a derivative, 3-allyl-β-lapachone is not deactivated [2]. This derivative is obtained only as a by-product in 4% yield and so has not been adequately studied.

This research was initiated to produce a derivative of β-lapachone which would not be deactivated and could be prepared synthetically from readily available starting materials. Lapachol is currently isolated from the heartwood of quite mature trees of some *Ipe* species (genus *Tabebuia*).

In an earlier investigation [4] β-lapachone was obtained using initially a photochemical reaction between 3-methylcrotonaldehyde and 1,4-naphthoquinone (47% yield), with no yield given for the last step.



Results and Discussion.

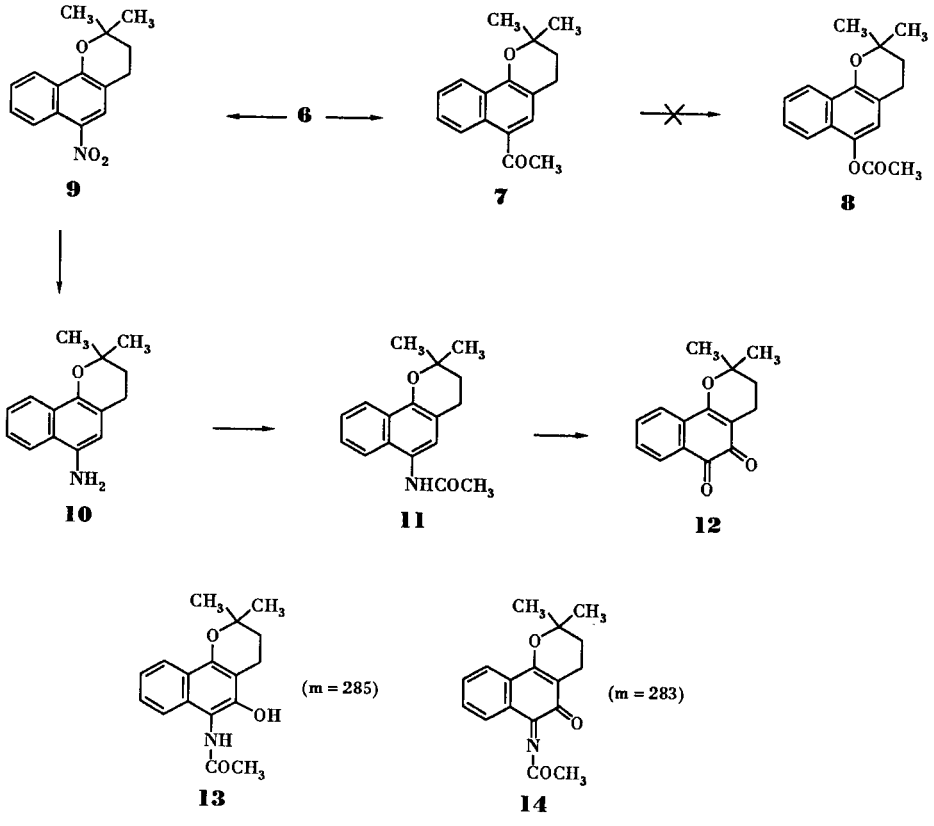
As a first reaction in our approach, α-naphthol was allowed to react with the acid chloride of 3-methylcrotonic acid. Although ester **1** is the initial product, it was not necessary to isolate this substance; the hydroxyketone **2** was obtained in 75% yield [5]. The cyclization of **2** could be effected by various acidic reagents and the best yield of ketone **3** (84%) was obtained with a mixture of formic and hydrochloric acids.

Some attempts were made to introduce an alkyl group adjacent to the carbonyl group of ketone **3**. However under the basic conditions necessary to form the anion, the pyran ring was opened to regenerate the anion of ketone **2**. The reduction with lithium aluminum hydride was readily accomplished. The resulting alcohol **4** was easily dehydrated under acid conditions and even washing with dilute acid, followed by chromatography yielded olefin **5**. The reduction of the double bond of **5** could be effected by hydrogenation using rather large amounts of catalyst and a low hydrogen pressure so that the naphthalene ring was not also reduced.

Both compounds **5** and **6** are natural products; **6** was first isolated from *Tectona granais* Linn [6] and both **5** and **6** were found in various Galium species [7]. These substances have also been synthesized in rather poor yield [8].

It was at first thought possible that a direct oxidation of **6** might yield β-lapachone. However, reaction with four different oxidizing agents produced in each case mixtures of substances with no indication of the formation of the desired *ortho*-quinone. Next the methyl ketone **7** was prepared with the idea of carrying out as the next step a Baeyer-Villiger reaction. The desired ketone was obtained in good yield by the reaction with acetyl chloride but the conversion to the naphthol acetate **8** was unsuccessful, giving a mixture of substances.

The nitration of **6** produced the expected nitration product **9** in excellent yield (95%). The reduction of **9** also



went very well but the resulting amine **10** rapidly darkened and so was converted to the more stable acetyl derivative **11**. When this derivative was treated with nitric acid with the expectation of obtaining a nitration product, the substance isolated turned out to be the desired β-lapachone **12** produced in quite reasonable yield.

The reaction of **11** with nitric acid for a short time yielded a mixture which had a component with the mass of the expected nitration product. However, on chromatography a major peak had a mass of 285 and on standing this changed to a mass of 283. A reasonable interpretation is that compound **13** was first formed and then slowly underwent air oxidation to **14**. Thus on longer contact with nitric acid, intermediate **14** could be hydrolyzed to produce β-lapachone.

Although these results could undoubtedly be improved at several steps the major objective has been achieved. β-Lapachone has been synthesized in an overall yield of 23% and the process can now be modified to give various derivatives with substituents in the heterocyclic ring.

EXPERIMENTAL

The melting points were obtained using the Kofler apparatus and are uncorrected. The nuclear magnetic resonance spectra were observed for hydrogen (200 MHz) and carbon 13 (50 MHz) using the Varian Gemini 200. The infra-red spectra were observed with Perkin Elmer models 137-B and 783. The mass spectra were observed using 70 eV with the Micromass 12F and the VG Autospec apparatus.

2-(1-Hydroxynaphthyl) Isobutenyl Ketone (**4**).

This ketone was prepared essentially as previously described [5] with a yield of 75%; ^{1}H nmr: 2.08 (s, 3H), 2.20 (s, 3H), 6.86 (s, 1H), 7.26 (m, 1H), 7.58 (m, 2H), 8.48 (m, 1H), 14.38 (s, 1H); ms: (m/z, relative intensity) 226 (M^+, 23), 211 (101).

2,2-Dimethylnaphtho[1,2-*b*]pyran-4-one (**3**).

Ketone **2** (150 mg, 0.66 mmole) was added to a hot (110°) solution of formic acid and concentrated hydrochloric acid (150 ml, 1:1). The solution was agitated for one hour at this temperature and then cooled and dichloromethane was added. The organic layer was separated, washed with water and dried over sodium sulfate and then concentrated. The crude product was purified by chromatography on silica gel and was removed from the column with hexane/ethyl acetate (9:1). There was obtained 123 mg (0.554 mmole, 84%) of product which melted at 76°; ir (potassium bromide): 3050, 2970, 2930, 1620, 1508, 780-665 cm^{-1}; ^{1}H nmr (deuteriochloroform): 8.33 (m, 1H, J = 8.3 Hz), 7.85 (m, 1H, J = 8.7 Hz), 7.79 (m, 1H, J = 7.8 Hz), 7.61 (m, 1H, J = 7.8, 8.3 Hz), 7.52 (m, 1H, J = 7.8, 8.3 Hz), 7.38 (m, 1H, J = 8.7 Hz), 2.82 (s, 2H), 1.60 (s, 6H); ms: (m/z, relative intensity), 226 (M^+, 56), 211 (79), 171 (62), 170 (100), 114 (52).

The high resolution ms (hrms): Calcd. for $C_{15}H_{14}O_2$: 226.0994. Found: 226.0979.

2,2-Dimethylnaphtho[1,2-*b*]pyran-4-ol (**4**).

A solution of ketone **3** (100 mg, 0.44 mmole) in tetrahydrofuran

(1.5 ml) was added drop by drop to lithium aluminum hydride (16.6 mg, 0.44 mmole) under nitrogen with agitation. After the addition was complete the mixture was stirred at reflux temperature for 30 minutes. After careful addition of a small amount of water, the mixture was filtered, the organic layer was dried over sodium sulfate and the solvent distilled. The product was purified by chromatography over silica gel being eluted with hexane-ethyl acetate (3:1). There was obtained 82.4 mg (82%) of alcohol **4** which melted with some decomposition at 104-108°.

The ms showed that water was readily eliminated; ms: 210 (13), 195 (88), 172 (100), 173 (31), 171 (31), 155 (18). The ^{1}H nmr had peaks at: 8.25 (m, 1H), 7.76 (m, 1H), 7.47 (m, 4H), 4.97 (m, 1H), 2.28 (dd, 1H), 1.82 (s, 1H), 1.55 (s, 2H), 1.40 (s, 3H).

The hrms Calcd. for $C_{15}H_{16}O_2$: 228.1150. Found: 228.1134.

2,2-Dimethylnaphtho[1,2-*b*]pyrene (**5**).

Ketone **3** was reduced as in the previous experiment using 25 mg of lithium aluminum hydride. The reaction mixture was decomposed by the dropwise addition of 6*N* hydrochloric acid. After the separation of the organic layer, drying and concentration, the dark oil was chromatographed on silica gel. Hexane eluted 77 mg (83%) of colorless oil which solidified on cooling [9]; ^{1}H nmr: 8.21 (m, 1H), 7.74 (m, 1H), 7.44 (m, 2H), 7.36 (d, 1H, J = 8.8 Hz), 7.46 (d, 1H, J = 8.8 Hz), 6.46 (d, 1H, J = 9.6 Hz), 5.66 (d, 1H, J = 9.6 Hz), 1.55 (s, 6H); ^{13}C nmr: 148.1 (C), 134.5 (C), 129.4 (CH), 127.7 (CH), 126.2 (CH), 125.3 (CH), 125.2 (C), 124.7 (CH), 122.9 (CH), 122.1 (CH), 119.9 (CH), 115.5 (C), 76.9 (C), 28.1 (2 CH_3).

3,4-Dihydro-2,2-dimethylnaphtho[1,2-*b*]pyran (**6**).

In a Parr hydrogenation bottle were placed 50 mg of palladium on carbon (10%) and tetrahydrofuran (20 ml). Then 50 mg of (0.24 mmole) of olefin **5** was added and the mixture was hydrogenated at 30 lbs pressure for 15 minutes. After filtration and evaporation of the solvent, there was obtained 50 mg (100%) of **6** as a colorless oil; ^{1}H nmr: 8.22 (m, 1H), 7.76 (m, 1H), 7.45 (m, 2H), 7.34 (d, 1H, J = 8.8 Hz), 7.18 (d, 1H, J = 8.8 Hz), 2.91 (t, 2H), 1.91 (t, 2H), 1.45 (s, 6H), ^{13}C nmr: 148.1 (C), 133.2 (C), 127.6 (CH), 127.2 (CH), 125.4 (C), 125.3 (CH), 124.7 (CH), 121.5 (CH), 118.7 (CH), 114.1 (C), 74.3 (C), 32.7 (CH_2), 26.8 (2 CH_3), 22.7 (CH_2).

6-Acetyl-3,4-dihydro-2,2-dimethylnaphtho[1,2-*b*]pyran (**7**).

Hydrocarbon **6** (134 mg, 0.63 mmole) in dichloromethane (1.8 ml) was added to a solution of titanium tetrachloride (0.63 mmole) in dichloromethane (1 ml). This solution under nitrogen was agitated while acetyl chloride (50 mg, 0.63 mmole) in dichloromethane (1 ml) at 0° was added. After two hours at 0° the mixture was treated with 10% hydrochloric acid. The organic layer was separated and the aqueous layer was extracted once with dichloromethane. The combined organic layer was dried over sodium sulfate and evaporated to dryness. The residue was chromatographed on silica gel and the product was extracted with hexane-ethyl acetate (9.4:0.6) to yield 107 mg (67%) of the acetyl derivative which melted at 106-114°; ir (potassium bromide): 2950, 1670, 1580, 8.35 cm^{-1}; ^{1}H nmr: 9.00 (m, 1H), 8.28 (m, 1H), 7.82 (s, 1H); 7.54 (m, 2H), 2.92 (t, 2H, J = 6.6 Hz), 2.70 (s, 3H), 1.95 (t, 2H, J = 6.6 Hz), 1.45 (s, 6H); ms: (m/z, relative intensity) 254 (100), 239 (38), 199 (91), 183 (50).

This substance was previously prepared in rather poor yield using boron trifluoride and acetic acid [9].

6-Nitro-3,4-dihydro-2,2-dimethylnaphtho[1,2-*b*]pyran (**9**).

Naphthopyran **6** (150 mg) and acetic acid (0.3 ml) were cooled in an ice-bath and concentrated nitric acid (48.6 mg) was added dropwise. After the addition, the mixture was placed in the refrigerator for 20 minutes and then was diluted with water. The yellow precipitate was filtered, washed with water and dried to yield 123.4 mg (95%) of nitration product **9** which melted at 135°; ir (potassium bromide): 2950, 1670, 1580, 835 cm^{-1}; ^{1}H nmr: 8.78 (m, 1H), 8.34 (m, 1H), 8.26 (s, 1H), 7.70 (m, 1H), 7.56 (m, 1H), 2.95 (t, 2H, J = 8.3 Hz), 1.98 (t, 2H, J = 8.3 Hz), 1.55 (s, 6H); ms: (m/z, relative intensity) 257 (M$^+$, 72), 202 (100), 171 (44), 128 (21).

The hrms Calcd. for $C_{15}H_{15}NO_3$: 257.1056. Found: 257.1052.

6-Acetylamino-3,4-dihydro-2,2-dimethylnaphtho[1,2-*b*]pyran (**11**).

To a mixture of nitro compound **9** (120 mg) and tin powder (240 mg) was added hydrochloric acid (1.2 ml) in three fractions. Then 1 ml of ethanol was added and the mixture heated at reflux temperature with intermitent agitation for 30 minutes. After cooling, neutralizing the acid and extracting with chloroform the organic layer was washed, dried and concentrated. The resulting amine weighed 96.2 mg and rapidly darkened in air; ir (film); 3600-3500, 3000-2900, 1650, 1480, 1430 cm^{-1}; ms: (m/z, relative intensity) 227 (M$^+$, 35), 172 (72), 171 (100), 140 (21).

This amine (96 mg) was treated with acetic anhydride (10 ml) and the mixture stirred on a water bath (~95°) for 10 minutes. The mixture was diluted with water and stirring continued to hydrolyze the excess anhydride. The product was extracted with chloroform and the solution washed with water and dried. Evaporation of the solvent left 100 mg of product which was washed with hexane to leave 95 mg (84%) of the amide which melted at 214-216°; ms: (m/z relative intensity), 269 (39), 213 (31), 172 (24), 171 (100).

The hrms Calcd. for $C_{17}H_{19}NO_2$: 269.1418. Found: 269.1427.

β-Lapachone (**12**).

A solution of amide **11** (95 mg) in glacial acetic acid (5 ml) was cooled in an ice-bath while concentrated nitric acid (34 mg) was added drop by drop. After the addition, the mixture was placed in the refrigerator for two hours and then diluted with water and extracted with ether. After washing with water and drying over sodium sulfate the solvent was evaporated. The crude product (80 mg) was chromatographed on a preparative layer of silica gel to yield 53 mg (62%) of product which was identical in all its spectral properties and melting point (140°) with β-lapachone prepared from lapachol; ir (potassium bromide): 2870, 1575, 1600, 1550, 1340, 1280, 1100, 1075, 920 cm^{-1}; ^{1}H nmr: 8.08 (m, 1H), 7.86 (m, 1H), 7.62 (m, 1H), 7.50 (m, 1H), 2.80 (t, 2H, J = 7.5 Hz), 1.85 (t, 2H, J = 7.5 Hz), 0.98 (s, 6H); ms: (m/z relative intensity) 242 (M$^+$, 15), 227 (17), 214 (42), 199 (16), 159 (100), 158 (42), 102 (24), 76 (30).

Acknowledgement.

We wish to thank the National Research Council of Brasil (CNPq) for financial support which made this work possible.

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