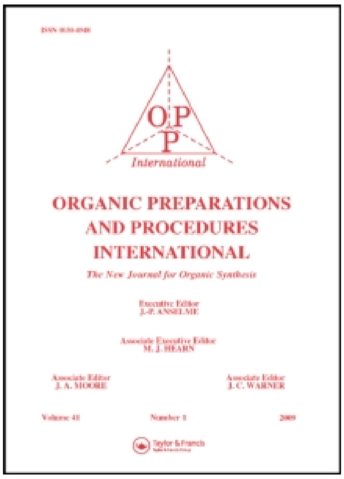

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

SYNTHESIS OF NEW NAPHTHALENE DERIVATIVES WITH POSSIBLE SCHISTOSOMICIDAL EFFECT. PART X

S. H. Doss[a]; S. S. A. Dimitry[ab]
[a] National Research Centre Dokki, Cairo, Egypt ARE [b] Chemistry Department, Brock University, St Catherines, Ontario, Canada

To cite this Article Doss, S. H. and Dimitry, S. S. A.(1981) 'SYNTHESIS OF NEW NAPHTHALENE DERIVATIVES WITH POSSIBLE SCHISTOSOMICIDAL EFFECT. PART X', Organic Preparations and Procedures International, 13: 2, 155 — 163

To link to this Article: DOI: 10.1080/00304948109356117

URL: http://dx.doi.org/10.1080/00304948109356117

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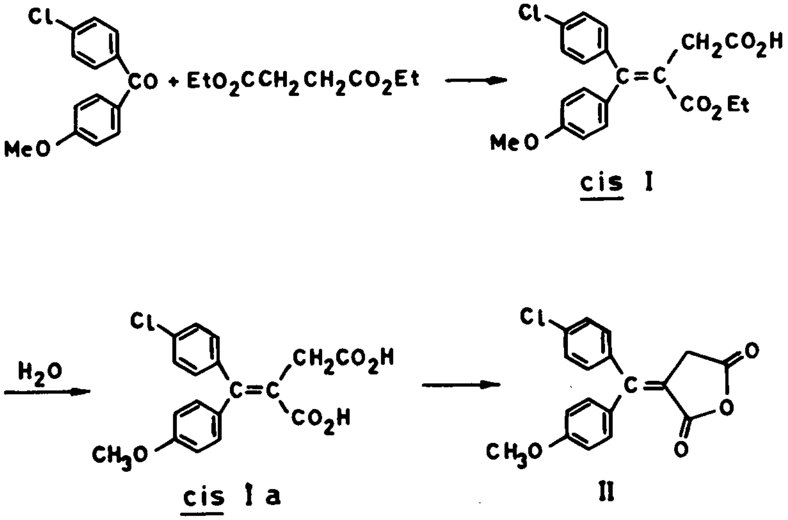
SYNTHESIS OF NEW NAPHTHALENE DERIVATIVES WITH POSSIBLE SCHISTOSOMICIDAL EFFECT. PART X[†]

Submitted by S. H. Doss* and S. S. A. Dimitry**
(5/4/79)

National Research Centre
Dokki
Cairo, Egypt - A.R.E.

It has been reported[1] that glycolysis and not oxidation metabolism is responsible for the survival of adult schistosomes and that naphthoquinones

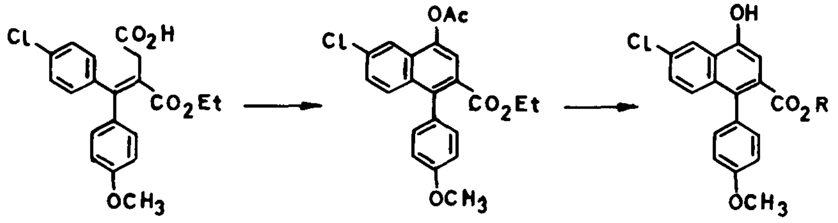


cis I

cis Ia

II

inhibit glycolysis of these organisms *in vitro*. Elslager *et al.*[2] synthesized naphthoquinone monooximes to overcome the lack of absorption of naphthoquinone and its inactivation by serum protein. They also prepared a number of [4-(aminoalkylamino)-1-naphthylazo] heterocycles.[3] The present work describes the synthesis of twelve new naphthalene derivatives. The Stobbe condensation of *p*-chloro-*p*-methoxybenzophenone with diethyl succinate gave a mixture of products (presumably geometrical isomers). Unfortu-

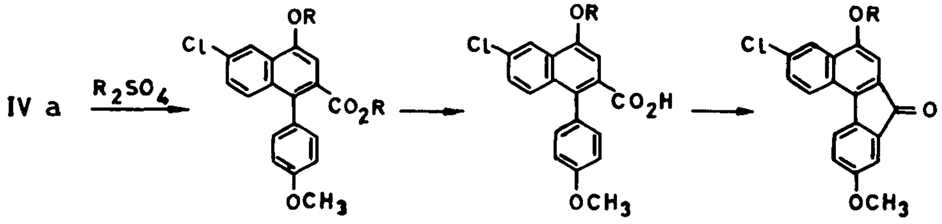


cis I

III

IV a,b

a) R = H , b) R = Me

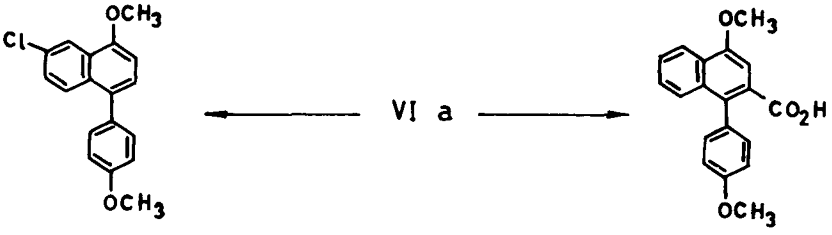


V a,b

VI a,b

VII a,b

a) R = Me , b) R = Et



VIII

IX

nately, attempts at separation of this mixture resulted only in the crystallization of cis-I, mp. 130-130.5° in 82.5% yield. The remaining oily product (17.5%) partially solidified after several days and crystallization of this solid from benzene afforded the diacid cis-Ia, mp. 237-238°. The structure of the remaining uncrystallized oil, which is possibly the trans-I half ester, is still under investigation. The cyclization of cis-I to III with acetic anhydride and sodium acetate indicated it to be the Z conformer;[4] III was further converted to IX, identical to an authentic sample.[5]

EXPERIMENTAL

All melting points are uncorrected. Infrared spectra were recorded by Sadtler Research Laboratories Inc., Philadelphia, PA on Beckman IR 4. NMR spectra were determined in $CDCl_3$ on a Varian A-60 spectrometer, with TMS as internal reference.

3-Carbethoxy-4-(p-chlorophenyl)-4-(p-anisyl)-3-butenoic acids (cis-I and trans-I).- To a stirred, boiling solution of potassium t-butoxide [from potassium (8.3 g., 0.2 mole) and t-butyl alcohol (200 ml, 3 moles)] was added powdered p-chloro-p'-methoxybenzophenone (24.6 g, 0.1 mole). It was then treated dropwise with diethyl succinate (17.4 g, 0.1 mole) over a period of 40 min., under nitrogen. The reaction mixture was refluxed further for 50 min., then acidified with ice cold dil. hydrochloric acid. The butanol was evaporated on a boiling water-bath under reduced pressure and the residue was extracted with ether. The ethereal layer was extracted with a saturated sodium bicarbonate solution and the oily acid (28.0 g, 75%) precipitated on acidification and solidified almost completely on standing for several days. This crude solid (7.5 g.) gave, after repeated crystallization from light petroleum (bp. 60-80°), 6.2 g. (82%) of pure crystalline cis-I, mp. 130-130.5°.

Anal. Calcd. for $C_{20}H_{19}ClO_5$: C, 64.08; H, 5.07; Cl, 9.47.

Found: C, 63.9; H, 5.2; Cl, 9.7.

IR(ν_{max}): 3300 (s, COOH), 1730 (vs, α,β-unsat. ester), 840 (s, 2 adjacent H) and 720 (m, C-Cl) cm^{-1}.

Evaporation of the mother liquor from the isolation of cis-I left an oily solid (1.3 g, 17.5%) which after several days partially solidified to give 0.2 g. of cis-Ia, mp. 237°; presumably the remaining oily residue (1.1 g.) is trans-Ia.

(Z) 3-Carboxy-4-(p-anisyl)-4-(p-chlorophenyl)-3-butenoic acid (cis-Ia).- The crude half ester (5 g.) was hydrolyzed by refluxing with 10% sodium hydroxide solution (50 ml) for 3 hrs. The alkaline solution was extracted with ether and the cold alkaline solution was acidified. The precipitated acid (4.15 g, 89.8%) was crystallized from ethanol or benzene, mp. 237°.

Anal. Calcd. for $C_{18}H_{15}ClO_5$: C, 62.33; H, 4.32; Cl, 10.24

Found: C, 62.55; H, 4.21; Cl, 10.4

$\nu_{max.}$: 3050 (s, COOH), 1690 (vs, dicarboxylic acid), 1400, 800 (m, 2 H adjacent) and 765 (s, C-Cl) cm^{-1}.

γ-(p-Anisyl)-γ-(p-chlorophenyl)itaconic anhydride (II).- The diacid (cis-Ia, 2 g, 0.0057 mole) was heated under reflux with a mixture of acetyl chloride (50 ml) and acetic anhydride (50 ml) for 1 hr, then worked up as usual[6] (yield 1.5 g, 79%). The anhydride was crystallized from benzene, mp. 240°.

Anal. Calcd. for $C_{18}H_{13}ClO_4$: C, 65.75; H, 3.95; Cl, 10.80

Found: C, 66.0; H, 4.0; Cl, 10.9

Ethyl 1-(p-anisyl)-4-acetoxy-6-chloro-2-naphthoate (III).- a) The crystalline half ester I (2.3 g.) was refluxed with acetic anhydride (10 ml) containing anhydrous sodium acetate (0.6 g.) for 5 hrs. The reaction mixture was worked up by removal of acetic anhydride under reduced pressure, addition of water and extraction of the precipitate with ether. The ethereal solution was washed with sodium bicarbonate solution then with water and dried (Na_2SO_4). Evaporation left 2.2 g, (83.6% of crude product which was crystallized from light petroleum (bp. 60-80°) to give III, mp. 127°.

Anal. Calcd for $C_{22}H_{19}ClO_5$: C, 66.3; H, 4.8

Found: C, 66.3; H, 4.9

ν_{max}: 1750 (s, $COOC_2H_5$), 1240 (vs), 1200 (vs, acetate) and 800 (m, C-Cl) cm^{-1}. b) Cyclization of the crude half ester.- The crude half ester I (8.0 g) was heated under reflux with acetic anhydride (33.0 ml) containing anhydrous sodium acetate (2.0 g.) for 5 hrs. The reaction mixture was worked up as before to yield 6.2 g (67.6%) of an oily brownish substance which failed to solidify, suggesting the presence of two cyclized isomers; their isolation and structure are still under investigation.

The carbonate layer gave after acidification, a solid (1.6 g, 18%) crystallized from benzene, mp. 237°, identified as the diacid (cis-Ia). An authentic sample was obtained by the hydrolysis of I.

Anal. Calcd. for $C_{18}H_{15}ClO_5$: C, 62.33; H, 4.32; Cl, 10.24

Found: C, 62.1; H, 4.2; Cl, 10.8

Attempts to crystallize the oily half ester (trans-I) using the same conditions or more severe ones were unsuccessful and yielded only a resinous substance.

1-(p-Anisyl)-4-hydroxy-6-chloro-2-naphthoic acid (IVa).- The acetoxy ester (III) (4.2 g, 0.010 mole) was refluxed with 10% sodium hydroxide for 2 hrs. and worked up as usual.[6] The phenolic acid (3.0 g, 86.7%) was crystallized from normal hexane or light petroleum (bp. 60-80°) into nearly colorless crystals mp. 233-234°.

Anal. Calcd. for $C_{18}H_{13}ClO_4$: C, 65.75; H, 3.95; Cl, 10.80

Found: C, 65.7; H, 3.9; Cl, 10.8

$\nu_{max.}$: 3500 (s, OH), 2950 (w, COOH), 1690 (vs. aryl COOH), 820 (s, two adjacent H) and 720 (s, C-Cl) cm^{-1}.

Ethyl 1-(p-anisyl)-4-ethoxy-6-chloro-2-naphthoate (Vb).- The phenolic acid (IVa 6 g, 0.018 moles) in dry acetone (100 ml) was refluxed with diethyl sulfate (7.9 g.) and anhydrous potassium carbonate (11 g.) for 12 hrs., then worked up as usual.[6] The product (7.0 g, 99.7%) was crystallized from light petroleum (bp. 60-80°) or hexane to give the ethoxy ester Vb, mp. 84-85°.

Anal. Calcd. for $C_{22}H_{21}ClO_4$: C, 68.66; H, 5.46; Cl, 9.23

Found: C, 68.5; H, 5.7; Cl, 9.6

$\nu_{max.}$ 1720 (vs. aryl ester) 835 (s, two adjacent H) 795 (m, C-Cl) cm^{-1}.

Methyl 1-(p-anisyl)-4-methoxy-6-chloro-2-naphthoate (Va) was similarly obtained using dimethyl sulfate in 85% yield from light petroleum (bp. 60-80°), mp. 98°.

Anal. Calcd. for $C_{20}H_{17}ClO_4$: C, 67.32; H, 4.76

Found: C, 67.5; H, 4.70

1-(p-Anisyl)-4-ethoxy-6-chloro-2-naphthoic acid (VIb).- Hydrolysis of the ethoxy ester (Vb, 2 g., ∿ 0.05 mole) with 10% sodium hydroxide gave rise to the ethoxy acid (1.6 g., 86.5%) crystallized from light petroleum (bp. 60-80°) into colorless needles, mp. 240°.

Anal. Calcd. for $C_{20}H_{17}ClO_4$: Cl, 9.95%. Found: Cl, 10.1

1-p-Anisyl-4-methoxy-6-chloro-2-naphthoic acid (VIa).- The methoxy ester (Va, 2 g., 0.0056 mole) was hydrolyzed with 10% sodium hydroxide, worked up as usual to give VIa (1.4 g., 73%), crystallized from light petroleum (bp. 60-80°), mp. 188°.

Anal. Calcd. for $C_{19}H_{15}ClO_4$: C, 66.56; H, 4.37; Cl, 10.36

Found: C, 66.6; H, 5.2; Cl, 10.4

9-Methoxy-5-ethoxy-3-chloro-7H-benz[c]fluoren-7-one (VIIb).- The ethoxy acid (VIb, 1.0 g., 0.0028 mole) was dissolved in 1,1,2,2-tetrachloroethane (30 ml.), then phosphorus oxychloride (1 ml) was added dropwise and the solution refluxed for 3 hrs. The solvent was removed by steam distillation and the remaining reddish brown solid (0.9 g., 95.7%) was crystallized from benzene as fine reddish crystals (0.8 g., 85%), mp. 204°.

Anal. Calcd. for $C_{20}H_{15}ClO_3$: C, 70.90; H, 4.43

Found: C, 70.52; H, 4.9

ν_{max} 1720 (vs, five-membered ring C=O), 829 (m, 2 adjacent H atoms), 782 (C-Cl) cm^{-1}.

9,5-Dimethoxy-3-chloro-7H-benz[c]fluoren-7-one (VIIa).- By the same method as described above, the methoxy acid VIa was cyclized into the fluorenone VIIa (yield 0.8 g, 85%), crystallized from benzene, mp. 214°.

Anal. Calcd. for $C_{19}H_{13}ClO_3$: C, 70.26; H, 4.00; Cl, 10.93

Found: C, 70.4; H, 4.1; Cl, 10.9

The nmr spectrum displayed two singlets at δ 3.98 (MeO on naphthalene ring) and 4.08 (MeO on phenyl ring) respectively. The two hydrogens between the carbonyl group and the two methoxy groups were assigned the peak at δ 8.2 while the two hydrogens at C_5 and C_7 of the naphthalene ring appeared at δ 8.51; the hydrogens at C_8 appeared at δ 8.46 while the two hydrogens of the benzene ring at C_5 and C_6 appeared at δ 8.30 and 8.37 respectively. The hydrazone of VIIa was prepared by a standard procedure and was obtained in 72% yield as an orange precipitate which was crystallized from benzene, mp. 172-173°.

Anal. Calcd. for $C_{20}H_{15}ClN_2O_2$: C, 68.47; H, 4.27

Found: C, 67.8; H, 4.35

ν_{max} 3400, 3250 (NH_2) 1620 (NH_2), 780 (m, C-Cl), three bands at 880, 850 and 690 (aromatic hydrogens) cm^{-1}.

1-p-Anisyl-4-methoxy-6-chloro-naphthalene (VIII).- The methoxy acid (VIa, 0.5 g., 0.0014 mole) was heated with copper bronze (0.5 g.) in an oil-bath at 180° for 2 hrs., and the product was extracted with ether and filtered. The ether was dried and evaporated. Crystallization from light petroleum (bp. 60-80°) gave 0.3 g. (69.7%), mp. 160° (shrinks at 126°).

Anal. Calcd. for $C_{18}H_{15}ClO_2$: C, 72.36; H, 5.02; Cl, 11.89

Found: C, 72.6; H, 5.1; Cl, 12.11

1-(p-Anisyl)-4-methoxy-2-naphthoic acid (IX).- The methoxy acid (VIa, 0.8 g., 0.0023 mole) was refluxed with tetralin (10 ml.) in the presence of palladized charcoal (0.5 g.) for 1 hr., according to the procedure of Baddar et al.[7]. The reaction mixture was cooled, diluted and extracted with saturated sodium carbonate solution; acidification of the basic aqueous extract gave 0.65 g. (91.5%) of IX. Recrystallization from light petroleum (bp. 60-80°) gave the analytical sample, mp. 212°.

Anal. Calcd. for $C_{19}H_{16}O_4$: C, 74.02; H, 5.12

Found: C, 74.2; H, 5.4

Methyl 1-p-anisyl-4-hydroxy-6-chloro-2-naphthoate (IVb).- The phenolic acid (IVa, 0.9 g., ∿ 0.0027 mole) was dissolved in absolute methyl alcohol (20 ml), dry hydrogen chloride gas was bubbled into the solution for 3 hrs. The solution was left standing overnight, then the alcohol was evaporated. Crystallization of the product from light petroleum (bp. 60-80°) gave 0.7 g., 75%) methyl ester, mp. 158°.

Anal. Calcd. for $C_{19}H_{15}ClO_4$: C, 66.56; H, 4.38; Cl, 10.36

Found: C, 66.70; H. 4.40; Cl, 10.8

Acknowledgement.- The authors thank Prof. Dr. F. G. Baddar, Kuwait University for suggesting interest and advice throughout the work, Dr. Latif, National Research Center for facilities provided and interest, Prof. Dr. V. B. Baghos, Faculty of Science, Cairo University for authentic samples provided, and Dr. H. Kober, Universität des Saarlandes for discussions.

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** Present address: Chemistry Department, Brock University, St. Catherines, Ontario, Canada.

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SULTAM DERIVATIVES WITH POSSIBLE SCHISTOSOMICIDAL ACTIVITY. NAPHTHOSULTAMS Part XIV

Submitted by S. H. Doss* and M. Hamed
(5/4/79)

National Research Centre
Dokki
Cairo, Egypt - A.R.E.

In continuation of our study of schistosomicidal agents,[1,2] we have synthesized some naphthosultams as shown in Schemes 1 and 2. The structure of *cis*-IIIb was established by its spectral data and by its cyclization to IV. Attempts to improve the yield of the Stobbe condensation, such as using sodium hydride, sodium methoxide, or changing the order of addition or increasing the molality of potassium *t*-butoxide were not en-