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Investigation on the Condensation of Dialdehydes with 2-Naphthol, 2-Thionaphthol and Dihydroxynaphthalenes

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Abstract: Condensation reactions of dialdehydes and naphthols have been carried out and the structures of the products have been investigated. Naphthofuronaphthofuran type compounds have been obtained in the case of using glyoxal and 2-naphthol or dihydroxynaphthalenes. Malonaldehyde and glutaraldehyde have resulted methano and propano-dinaphtho[1,3]dioxocins respectively. In the case of 2-thionaphthol, different to those obtained from 2-naphthol and dihydroxynaphthalenes, naphthothiophene and naphthothiopyran derivatives have been isolated. Mechanisms of the reactions and the difference between the products have been discussed.

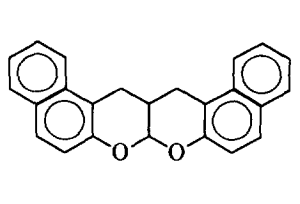
INTRODUCTION

7a,15a-dihydro-naphtho[2,1-b]naphtho[1',2':5,6]pyrano[3,2-e]pyran **1**,[1] angular derivatives of **1** such as 7a,15a-dihydro-7a-methyl-naphtho[2,1-b]naphtho[1',2':5,6]pyrano[3,2-e]pyran **2**, 7a,15a-dihydro-7a-methyl-15a-isopropyl-naphtho[2,1-b]naphtho[1',2':5,6]pyrano[3,2-e]pyran **3**[2] and 2,2'-dimethyl-3,3'-spirobi[2,3-dihydro-1H-naphtho[2,1-b]pyran] **4**[3] have been produced earlier. Compounds **2**, **3** and **4** have been synthesized in one step although the synthesis of **1** has only been achieved by several steps.

7a,14c-dihydro-naphtho[2,1-b]naphtho[1',2':4,5]furo[3,2-d]furan **5**,[4] and its angular monoalkyl derivative 7a,14c-dihydro-7a-methyl-naphtho[2,1-b]naphtho[1',2':4,5]furo[3,2-d]furan **6**[5] have also been synthesized before by the reaction of 2-naphthol with glyoxal and methylglyoxal respectively. Angular dialkyl derivatives of **5** have been produced by Claisen rearrangement of 1,4-bis(aryloxy)-2-butynes.[6] However, monoalkyl derivatives of **5** could not be produced with this method.

Compounds **2**, **3** and **4** have been chosen for their potential anti-cancer and anti-AIDS properties and have been tested at National Cancer Institute - USA. However none have shown encouraging biological activity.

In this work, naphthofuronaphthofuran, dinaphtho[1,3]dioxocin and dinaphtho[1,3]dithiocin derivatives with new functional groups have been synthesized in order to increase their possible biological activities.



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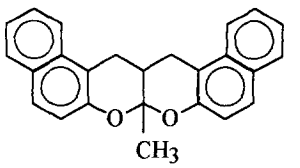

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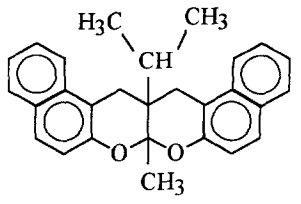

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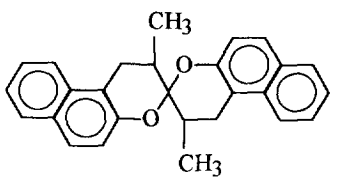

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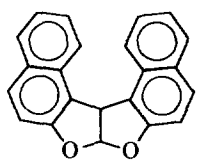

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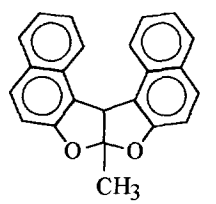

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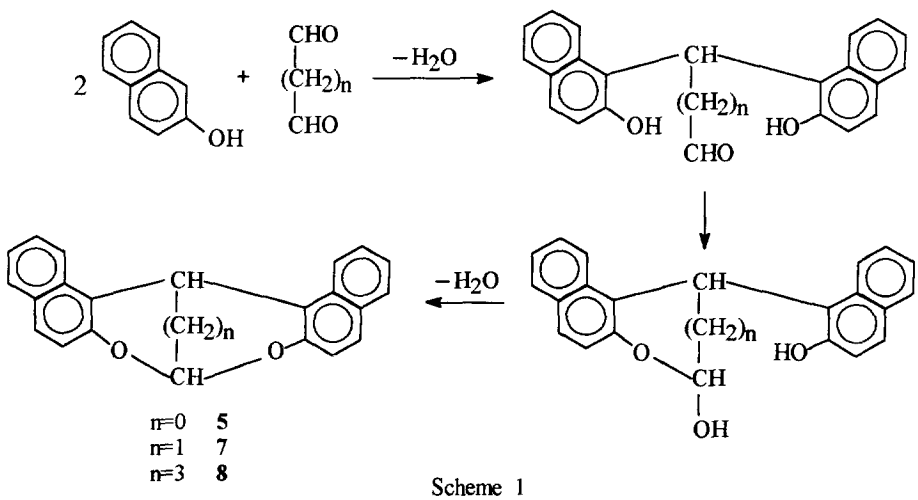
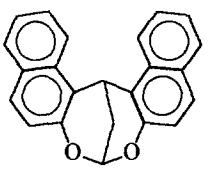
RESULTS AND DISCUSSIONS

Condensation of glyoxal and malonaldehyde with 2-naphthol in the presence of mild acids gave naphthofuronaphthofuran **5** and methano-dinaphtho[1,3]dioxocin **7** type compounds respectively.[4,7] The reaction proceeds via condensation of two moles of 2-naphthol with one carbonyl group of dialdehyde, followed by intramolecular acetalization reaction (scheme 1).

Similar reaction of 2-naphthol with glutaraldehyde has been achieved in this work and propano-dinaphtho-[1,3]dioxocin type compound **8** has been produced in good yield.



Scheme 1



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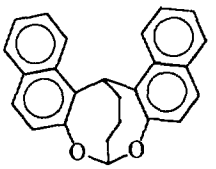


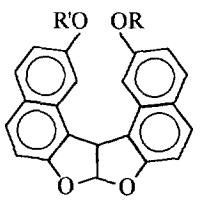
8

Condensation reactions of dihydroxynaphthlenes and dialdehydes have resulted in either dimeric or polymeric products depending on the positions of the hydroxyl groups. 2,7-Dihydroxynaphthalene has reacted with glyoxal and **9a**[8] has been formed. However its reaction products with malonaldehyde and glutaraldehyde have been ladder type polymers.[9] This is probably due to the steric effect. Once, furofuran type structure is formed (**9a**) and the second condensation reaction of two naphthol rings with glyoxal is sterically hindered. In the case of malonaldehyde and glutaraldehyde, the steric hindrance is diminished and -14 position of the dioxocin compound which bears the hydroxyl group is opened to second condensation with carbonyl groups and polymer formation occurred.

2,3-Dihydroxynaphthalene has shown the same behaviour as 2,7-dihydroxynaphthalene and dimeric product **10a** has been obtained by he reaction with glyoxal. However, its reaction with malonaldehyde and glutaraldehyde have resulted polymeric products.[9]

Dimeric products could not be obtained by the reactions of glyoxal with 2,6- and 1,5-dihydroxynaphthalenes, only polymers have formed.[10] Monomethylether derivative of 1,5-dihydroxynaphthalene has been prepared in order to overcome condensation polymerization, then the dimeric products **11** and **12** have easily been produced. Furthermore, methoxy (**9b**), acetoxy (**9c** and **10b**) and benzoxy (**9d** and **10c**) derivatives have also been prepared by methylation, acetylation and benzoylation of **9a** and **10a** respectively.

Two hydroxyl groups of **10a** have been derivatized while only one hydroxyl group of **9a** could be converted to corresponding derivatives. As explained earlier, this may be due to the steric hindrance of two naphthol rings. This has been supported by the evidence that no product could be isolated from the reaction of 2-hydroxy-7-methoxynaphthalene and glyoxal.



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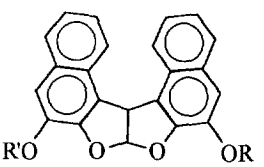
(a) R=R'= -H
(b) R= -H R'= - CH_3
(c) R= -H R'= - $COCH_3$
(d) R= -H R'= - COC_6H_5



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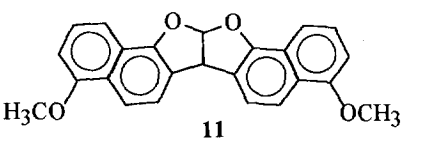
(a) R=R'= -H
(b) R=R'= - $COCH_3$
(c) R=R'= - COC_6H_5



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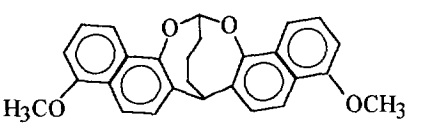

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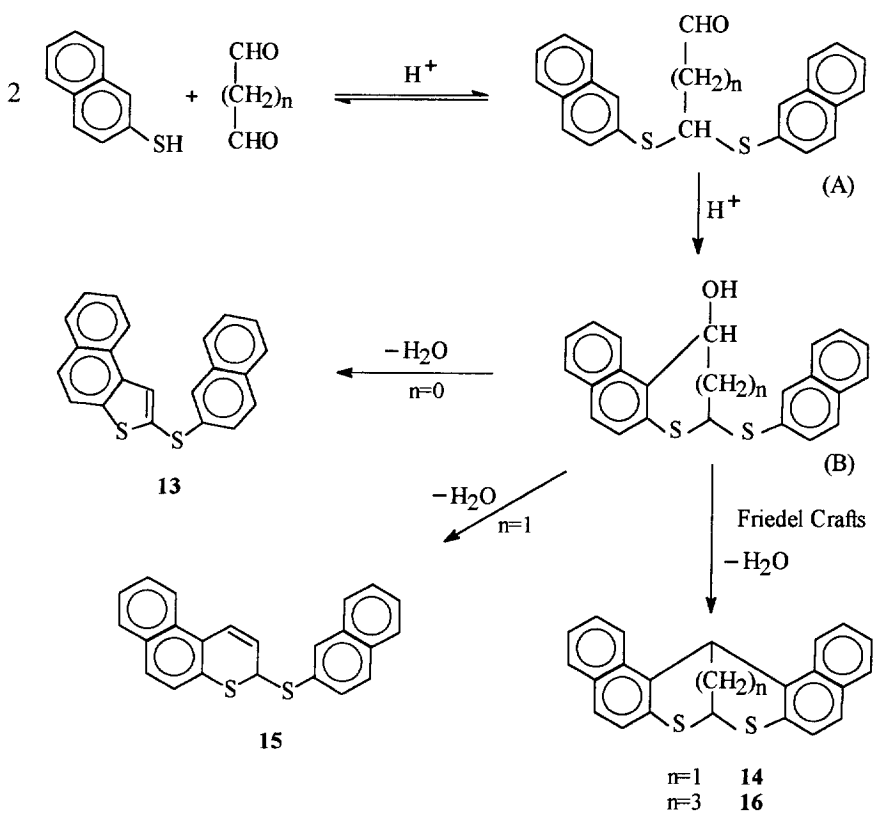
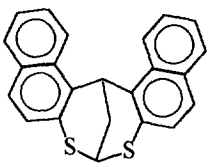
The reaction products of 2-thionaphthol with dialdehydes have been completely different. The naphthothiophene derivative **13** has formed from glyoxal. Also a mixture of dinaphtho[1,3]dithiocin **14** and naphthothiopyran **15** derivatives have been obtained by the reaction of malonaldehyde. However the product of glutaraldehyde has been similar to that produced from 2-naphthol and dinaphtho[1,3]dithiocin type compound **16** has been obtained. This difference has obviously been due to the reaction pathway. The purposed mechanism is shown in scheme 2.

Thioacetalization reaction of two moles of 2-thionaphthol and one of carbonyl groups of dialdehyde compound have probably occured first and the intermediate dithioacetal (A) has formed. This type of reaction between dicarbonyl compounds and thiophenol has been achieved before.[11,12] Furthermore, monothiohemiacetals have easily been prepared from glyoxals and thiols.[13] Intramolecular Friedel-Crafts type reaction of intermediate (A) has probably occured and the intermediate (B) has formed. In the case of n=0, elimination of one mole of water has produced the compound **13** since the intramolecular Friedel-Crafts reaction has not been sterically favoured. In the case of n=1, both water elimination and Friedel-Crafts reaction have proceeded together to give a mixture of the compounds **14** and **15**. In the case of n=3, only Friedel-Crafts reaction has occured and the bicyclo compound **16** has been produced.



Scheme 2



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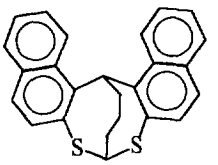

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It is well known that hemiacetal and acetal formations are much easier when thiophenol is used in place of phenol. this is the reason why the reaction of 2-thionaphthol and 2-naphthol have shown completely different pathways with dialdehydes. In the case of 2-naphthol, first Friedel-Crafts then intramolecular acetalization occurs whereas 2-thionaphthol prefers first thioacetalization reaction with dialdehydes.

EXPERIMENTAL

General Methods: IR spectra have been run on Jasco FT-IR 5300 spectrometer. ^{1}H-NMR have been recorded by a 200 MHz Bruker instrument using TMS as an internal standart. Mass spectra have been measured by DS-55 model instrument at East Anglia University.

Synthesis of Aldehydebisulphites: Glyoxalbisulphite, malonaldehydebisulphite and glutaraldehydebisulphite have been prepared by reaction of 30% solution of sodiumbisulphite with corresponding dialdehydes in 2/1 mole ratio. Bisulphite adducts have been precipitated by addition of ethanol to the solution.

Synthesis of Monomethylether Derivatives of Dihydroxynaphthalenes: 2-Hydroxy-7-methoxynaphthalene[14] and 1-hydroxy-5-methoxynaphthalene[15] have been prepared as described in corresponding references. 2-Hydroxy-7-methoxynaphthalene has been recrystallized from ligroin, m.p.=116-117°C. 1-Hydroxy-5-methoxynaphthalene has been recystallized from iso-octane, m.p.=134-135°C.

Procedure of Methylation: 1 mole of dihydroxynaphthofuronaphthofuran compound has been dissolved in 0.1 M NaOH solution and 1 mole of dimethylsulfate has been added to the solution. The reaction mixture has been stirred at room temperature for 4 h. Precipitated part has been washed with water and crystallized from appropriate solvent.

Procedure of Acetylation: 1 mole of dihydroxynaphthofuronaphthofuran compound has been solved in dry acetone and pyridine has been added to the solution. 2 moles of acetylchloride solution in dry acetone has been dropped to the solution slowly and the reaction mixture has been stirred at room temperature for 6 h. Precipitated part has been washed with water and recrystallized from appropriate solvents.

Procedure of Benzoylation: 1 mole of dihydroxynaphthofuronaphthofuran compound has been dissolved in dry acetone and pyridine has been added to the solution. 2 moles of benzoylchloride solution in dry acetone has been dropped to the solution slowly and the reaction mixture has been stirred at room temperature for 6 h. Precipitated part has been washed with water and recrystallized from appropriate solvents.

Standart Method: 2 moles of naphthol compound has been dissolved in 98% formic acid and has been heated to 50-60°C. 1 mole of aldehydebisulphite has then been added to the solution and stirred at that temperature for 4 h. Reaction mixture has been poured into water and the precipitated part has been filtered.

The crude product has been washed with water till neutralizing occured and has been boiled in water to remove the unreacted naphthol. Reaction products have been purified by appropriate methods.

8,16-Methano-16H-dinaphtho[2,1-d:1',2'-g][1,3]dioxocin (7):

This compound has been obtained from the reaction of 2-naphthol with malonaldehyde and purified by recrystallizing from acetone-ethanol (1/1, v/v) mixture. m.p.=220-222°C, 23% yield. IR(KBr): 3000-2900, 1240, 1170, 1070 cm^{-1}. ^{1}H-NMR($CDCl_3$): 5.4 (1H, t, 16-H), 6.3 (1H, t, 8-H), 2.5 (2H, dd, J=2.1 and 0.9 Hz, -CH_2), 7.1-8.0 (12H, m, aromatics). MS: m/e=281, 168, 43, 28(100%).

8,16-Propano-16H-dinaphtho[2,1-d:1',2'-g][1,3]dioxocin (8):

this compound has been obtained from the reaction of 2-naphthol with glutaraldehyde and purified by boiling in ligroin. m.p.=230-232°C, 21% yield. IR(KBr): 3000-2900, 1240, 1160, 1070 cm^{-1}. ^{1}H-NMR (acetone-d_6): 5.4 (1H, t, 16-H), 7.4 (1H, t, 8-H), 1.5-2.5 (6H, m, -CH_2), 7.0-8.2 (12H, m, aromatics). MS: m/e=296, 281, 205, 168, 43(100%).

2,13-Dihydroxy-7a,14c-dihydro-naphtho[2,1-b]naphtho[1',2':4,5]furo[3,2-d]furan (9a):

This compound has been obtained from the reaction of 2,7-dihydroxynaphthalene with glyoxal and purified by recrystallizing from glacial acetic acid. m.p.=295-296°C (decomp.), 78% yield. IR(KBr): 3400-3300, 1260, 1130, 1060 cm^{-1}. ^{1}H-NMR($CDCl_3$): 5.5 (1H, d, J=5.7 Hz, 14c-H), 7.1 (1H, d, J=6.0 Hz, 7a-H), 8.7 (2H, s, -OH), 7.0-8.2 (10H, m, aromatics). MS: M^+=342(100%), m/e=313, 184, 171, 160, 43.

2-Hydroxy-13-methoxy-7a,14c-dihydro-naphtho[2,1-b]naphtho[1',2':4,5]furo[3,2-d]furan (9b):

This compound has been obtained from the reaction of **9a** with dimethylsulfate and purified by recrystallizing from petroleum ether. m.p.=250-257°C (decomp.), 76% yield. IR(KBr): 3400-3300, 3000-2900, 1260, 1130, 1060 cm^{-1}. ^{1}H-NMR(acetone-d_6): 5.7 (1H, d, J=5.8 Hz, 14c-H), 7.2 (1H, d, J=5.8 Hz, 7a-H), 8.7 (1H, s, -OH), 3.8 (3H, s, -OCH_3), 6.8-8.0 (10H, m, aromatics).

2-Hydroxy-13-acetoxy-7a,14c-dihydro-naphtho[2,1-b]naphtho[1',2':4,5]furo[3,2-d]furan (9c):

This compound has been obtained from the reaction of **9a** with acetylchloride. m.p.=297-299°C, 96% yield. IR(KBr): 3410, 1740, 1260, 1130, 1060 cm^{-1}. ^{1}H-NMR(DMSO-d_6): 5.7 (1H, d, J=6.0 Hz, 14c-H), 7.2 (1H, d, J=6.0 Hz, 7a-H), 9.7 (1H, s, -OH), 2.3 (3H, s, -$OCOCH_3$), 6.9-8.2 (10H, m, aromatics). MS: M^+=384, m/e=342, 313, 184, 43(100%).

2-Hydroxy-13-benzoxy-7a,14c-dihydro-naphtho[2,1-b]naphtho[1',2':4,5]furo[3,2-d]furan (9d):

This compound has been obtained from the reaction of **9a** with benzoylchloride and purified by recrystallizing from toluene. m.p.=290-292°C, 94% yield. IR(KBr): 3350, 1720, 1260, 1130, 1060 cm^{-1}. ^{1}H-NMR(DMSO-d_6): 5.7 (1H, d, J=6.0 Hz, 14c-H), 7.2 (1H, d, J=6.1 Hz, 7a-H), 9.5 (1H, s, -OH), 6.9-8.4 (15H, m, aromatics). MS: M^+=446, m/e=184, 171, 160, 105(100%).

6,9-Dihydroxy-7a,14c-dihydro-naphtho[2,1-b]naphtho[1',2':4,5]furo[3,2-d]furan (10a):

This compound has been obtained from the reaction of 2,3-dihydroxynaphthalene with glyoxal. m.p.=220-222°C (decomp.), 72% yield. IR(KBr): 3400-3300, 1290, 1110, 1060 cm^{-1}. ^{1}H-NMR(DMSO-d_6): 5.8 (1H, d, J=5.9 Hz, 14c-H), 7.3 (1H, d, J=6.1 Hz, 7a-H), 10.1 (2H, s, -OH), 7.2-8.4 (10H, m, aromatics). MS: M^+=342, m/e=313, 184, 171, 160(100%).

6,9-Diacetoxy-7a,14c-dihydro-naphtho[2,1-b]naphtho[1',2':4,5]furo[3,2-d]furan (10b):

This compound has been obtained from the reaction of **10a** with acetylchloride and purified by recrystallizing from ethanol. m.p.=174-176°C, 93% yield. IR(KBr): 1760, 1290, 1110, 1060 cm^{-1}. ^{1}H-NMR

(DMSO-d_6): 6.1 (1H, d, J=5.8 Hz, 14c-H), 7.3 (1H, d, J=5.7 Hz, 7a-H), 2.3 (6H, s, -OCOCH$_3$), 7.1-8.4 (10H, m, aromatics). MS: M^+=446, m/e=184, 160(100%), 43.

6,9-Dibenzoxy-7a,14c-dihydro-naphtho[2,1-b]naphtho[1',2':4,5]furo[3,2-d]furan (10c):

This compound has been obtained from the reaction of **10a** with benzoylchloride and purified by boiling in ethanol. m.p.=264-266°C, 88% yield. IR(KBr): 1740, 1290, 1110, 1060 cm^{-1}. ^{1}H-NMR(DMSO-d_6): 6.2 (1H, d, J=5.8 Hz, 14c-H), 7.2 (1H, d, J=5.8 Hz, 7a-H), 7.1-8.6 (20H, m, aromatics). MS: m/e=184, 171, 160, 105(100%).

4,9-Dimethoxy-6b,13a-dihydro-naphtho[1,2-b]naphtho[1',2':5,4]furo[3,2-d]furan (11):

This compound has been obtained from the reaction of 1-hydroxy-5-methoxynaphthalene and purified by column chromatography (eluent: toluene). m.p.=210-212°C (decomp.), 54% yield. IR(KBr): 3000-2800, 1260, 1150, 1060 cm^{-1}. ^{1}H-NMR(DMSO-d_6): 5.2 (1H, d, J=5.6 Hz, 6b-H), 6.8 (1h, d, J=5.8 Hz, 13a-H), 3.9 (6H, s, -OCH$_3$), 6.9-8.0 (10H, m, aromatics). MS: M^+=370(100%), m/e=184, 160.

4,10-Dimethoxy-7,15-propano-7H-dinaphtho[1,2-d:2',1'-g][1,3]dioxocin (12):

This compound has been obtaine from the reaction of 1-hydroxy-5-methoxynaphthalene with glutaraldehyde and purified by boiling in iso-octane. m.p.=190-192°C, 21% yield. IR(KBr): 3000-2800, 1260, 1120, 1050 cm^{-1}. ^{1}H-NMR($CDCl_3$): 5.1 (1H, t, 7-H), 3.9 (6H, s, -OCH$_3$), 1.5-2.5 (6H, m, -CH$_2$), 6.5-8.0 (11H, m, 15-H+aromatics).

2-Naphtho[2,1-b]thienylnaphthylsulfide (13):

This compound has been obtained from the reaction of 2-thionaphthol with glyoxal and purified by boiling in ethanol. m.p.=155-157°C, 63% yield. IR(KBr): 1190, 1160, 1000 cm^{-1}. ^{1}H-NMR($CDCl_3$): 7.4-8.4 (13H, m, aromatics). MS: M^+=342, m/e=318, 184, 160, 115(100%).

8,16-Methano-16H-dinaphtho[2,1-d:1',2'-g][1,3]dithiocin (14):

This compound has been obtained from the reaction of 2-thionaphthol with malonaldehyde and has been seperated from the solid mixture containing **15** by solubility difference in boiling diethylether. Dissolved part has been cooled and **14** has obtained and purified by recrystallizing from diethylether. m.p.=169-171°C, 12% yield. IR(KBr): 1210, 1140, 1120, 1070 cm^{-1}. ^{1}H-NMR($CDCl_3$): 5.4 (1H, t, 16-H), 5.6 (1H, dd, J=3.1 and 8.9 Hz, 8-H), 2.8 (1H, dt, J=3.3 and 13.8 Hz, 17-H, axial), 2.2 (1H, td, J=2.2 and 11.5 Hz, 17-H, equatorial), 7.1-8.3 (12H, m, aromatics). MS: m/e=197, 165, 149(100%).

2-3H-naphtho[2,1-b]thiopyranylnaphthylsulfide (15):

This compound has been obtained from the reaction of 2-thionaphthol with malonaldehyde. In above experiment the insoluble part has been boiled in diethylether to remove the remained **14** and **15** has been purified. m.p.=108-110°C, 10% yield. IR(KBr): 1195, 1140, 1080 cm^{-1}. ^{1}H-NMR($CDCl_3$): 6.3 (1H, d, J=8.45 Hz, 9-H), 5.9 (2H, m, 18-H, 17-H), 7.1-8.2 (13H, m, aromatics). MS: M^+=356, m/e=297, 197, 165, 147(100%).

8,16-Propano-16H-dinaphtho[2,1-d:1',2'-g][1,3]dithiocin (16):

This compound has been obtained from the reaction of 2-thionaphthol and glutaraldehyde and purified by boiling in ethanol. m.p.=106-107°C, 18% yield. IR(KBr): 3000-2900, 1190, 1130, 1010 cm^{-1}. ^{1}H-NMR($CDCl_3$): 4.6 (1H, t, 16-H), 1.8-2.4 (6H, m, -CH2), 7.3-8.1 (13H, m, 8-H+aromatics). MS: M^+=384, m/e=318, 226, 184, 160(100%), 115.

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