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A NEW ROUTE TO HYDROPHENANTHRENE RING SYSTEM INVOLVING ARYL PARTICIPATED INTRAMOLECULAR CYCLISATION OF DIAZOMETHYL KETONES

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ABSTRACT : The tricyclic enones **4** and **5** have been synthesised involving acid catalysed intramolecular cyclisation of the diazomethyl ketones **1** and **2** respectively. The present synthesis constitutes a new route to hydrophenanthrene ring system.

Hydrophenanthrene nucleus is present in a large number of natural products. Widespread interest in hydrophenanthrenes is reflected in a number of diverse synthetic approaches[1] to these compounds. In connection with our interest in the synthesis of natural products, we have studied aryl participated intramolecular cyclisation of appropriately substituted diazomethyl ketones as an expedient pathway to hydrophenanthrene framework. Thus, acid-induced intramolecular cyclisation of the diazomethyl ketones **1** and **2** afforded the enediones **4** and **5** respectively in moderate yields. A similar enedione incorporating a gem-dimethyl group at C-1, e.g. **6**, would be a useful intermediate for the synthesis of

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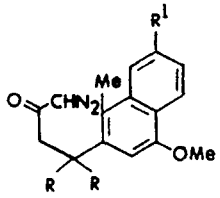

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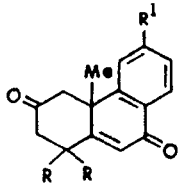

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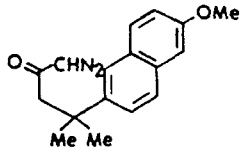

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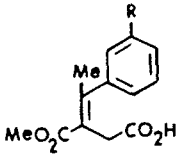

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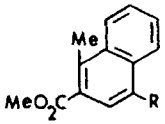

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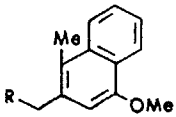

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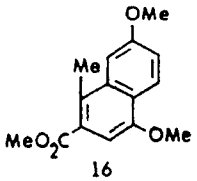
14, R = $CH(CO_2Et)_2$
15, R = CH_2CO_2H



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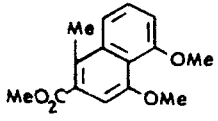

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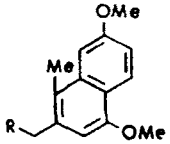

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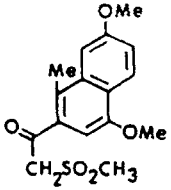
19, R = Br
20, R = $CH(CO_2Et)_2$
21, R = CH_2CO_2H



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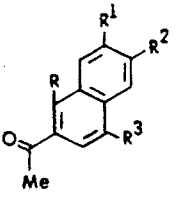

23, R = R^1 = R^3 = H
R^2 = OMe
24, R = Me, R^2 = H
R^1 = R^3 = OMe

ring C-aromatic tricyclic diterpenes since catalytic hydrogenation of **6** would generate[2] the required trans-stereochemistry at the A/B ring juncture. The present method for the synthesis of hydrophenanthrene ring system is convenient since the starting materials are readily accessible and the enediones are easily isolated from the crude reaction products through chromatography on silica gel.

Stobbe condensation of acetophenone with dimethyl succinate in the presence of sodium hydride according to the reported procedure[3] afforded the half acid-ester **8**. The compound **8** underwent intramolecular cyclisation on being heated with acetic anhydride in the presence of sodium acetate[4] to furnish the acetoxy-ester **10** in good yield. Deacetylation of **10** followed by methylation of the resulting product afforded the ester **11** in 72% overall yield. Reduction of **11** with lithium aluminium hydride furnished the primary alcohol **12** which on treatment with phosphorous tribromide was converted into the bromide **13**. Reaction of the bromide with diethyl sodiomalonate in benzene provided the diester **14** in good yield. Alkaline hydrolysis of **14** followed by thermal decarboxylation of the resulting diacid furnished the crystalline acid **15**. The acid chloride, prepared from **15** with oxalyl chloride, was treated with an excess of diazomethane in ether to afford the diazoketone **1** in excellent yield. On treatment with trifluoroacetic acid (TFA) in methylene chloride at -20°C, the diazoketone **1** underwent intramolecular cyclisation to furnish the crystalline enedione **4** in 52% yield.

A similar sequence of reactions was used to synthesise the enedione **5**. 3-Methoxyacetophenone was condensed with dimethyl succinate in the presence of sodium hydride[3] and the resultant half acid-ester **9** was cyclised by treatment with a mixture of acetic anhydride and sodium acetate. Deacetylation of the product followed by methylation and chromatographic separation afforded the methyl esters **16** (31% from **9**) and **17** (9% from **9**). Reduction of the ester **16** with lithium aluminium hydride followed by treatment of the resulting alcohol **18** with PBr_3 furnished the bromide **19**. Reaction of **19** with diethyl sodiomalonate afforded the diester **20** in good yield. Hydrolysis of **20** followed by decarboxylation of the resulting diacid afforded the crystalline acid **21** in high yield. The corresponding diazomethyl ketone **2**, prepared from the acid chloride of **21** with CH_2N_2, was treated with TFA in methylene chloride at -25°C to furnish the enedione **5** in 50% yield.

The diazoketone **7** has been easily prepared[5] from the naphthyl methyl ketone **23**. For the synthesis of the diazoketone **3**, we have now prepared the naphthyl methyl ketone **24** from the naphthoic ester **16**. Reaction of **16** with dimethyl sulphone anion[6] in DMSO yielded the β-ketosulphone **22**. Reductive cleavage of the crude product with zinc dust afforded the desired ketone **24** in 75% overall yield.

EXPERIMENTAL

Melting and boiling points are uncorrected. Melting points were taken in open capillaries in a sulphuric acid bath. IR

spectra were recorded on a Perkin-Elmer 298 infrared spectrophotometer. ^{1}H NMR spectra were recorded on Varian T-60A and Varian XL-200 spectrometers. Peak positions are indicated in ppm downfield from internal TMS. All reactions were carried out in nitrogen atmosphere. Extracts were dried over anhydrous Na_2SO_4. Light petroleum refers to the fraction of b.p. 60-80°C and ether refers to diethyl ether.

Methyl 4-acetoxy-1-methyl-2-naphthoate (10) : To a solution of **8**[3] (6 g, 26 mmol) in Ac_2O (30 ml) was added NaOAc (2.5 g, 30 mmol) and the mixture was refluxed for 6 h. It was then cooled, diluted with water, and extracted with chloroform. The organic extract was washed with aqueous $NaHCO_3$ and water, dried and concentrated. The residue was crystallised from acetone-light petroleum to furnish the acetoxy-ester **10** (4.96 g, 75%), m.p. 73-74°C; IR (KBr): 1760, 1718, 1620, 1602 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ2.35 (s, 3H), 2.84 (s, 3H), 3.88 (s, 3H), 7.42-8.25 (m, 5H). Anal. calcd. for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found : C, 69.90; H, 5.65.

Methyl 4-methoxy-1-methyl-2-naphthoate (11) : A solution of **10** (4.5 g, 17 mmol) and p-toluenesulphonic acid (500 mg, 3 mmol) in MeOH (80 ml) was refluxed for 5 h and then cooled, diluted with water, and extracted with ether. The ethereal extract was washed with aqueous $NaHCO_3$ and water, dried, and concentrated. The residue (3.5 g) was dissolved in 1,2-dimethoxyethane (25 ml), anhydrous K_2CO_3 (2.8 g, 20 mmol) and MeI (4.3 g, 30 mmol) were added, and the mixture was refluxed with stirring for 10 h. It was then cooled, diluted with water, and extracted with ether. The ethereal extract was washed with cold aqueous NaOH (4%) and water, dried, and concentrated. The residue was crystallised from acetone-light petroleum to furnish the ester **11** (2.9 g, 72%), m.p. 104-105°C; IR (KBr) : 1718, 1618, 1593 cm^{-1}; ^{1}H NMR (CCl_4): δ 2.70 (s, 3H), 3.91 (s, 6H), 7.12 (s, 1H), 7.42-7.60 (m, 2H), 7.90-8.38 (m, 2H). Anal. calcd. for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found : C, 73.11; H, 6.24.

2-Hydroxymethyl-4-methoxy-1-methylnaphthalene (12) : The ester **11** (2.5 g, 11 mmol) was reduced with $LiAlH_4$ (0.76 g, 20 mmol) in anhydrous ether (50 ml) to afford the alcohol **12** (2.1 g, 96%), m.p. 109-110°C (from ether-light petroleum); ^1H NMR ($CDCl_3$): δ 2.49 (s, 3H), 2.66 (bs, 1H), 3.90 (s, 3H), 4.67 (s, 2H), 6.73 (s, 1H), 7.27-7.50 (m, 2H), 7.77-8.25 (m, 2H). Anal. calcd. for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found : C, 77.28; H, 7.20.

3-(4-Methoxy-1-methyl-2-naphthyl)propanoic acid (15) : Phosphorus tribromide (1 g, 3.7 mmol) in benzene (3 ml) was added dropwise at 0°C to a stirred solution of the alcohol **12** (2 g, 10 mmol) in benzene (10 ml). The mixture was stirred at 50°C for 2 h, cooled, diluted with water, and extracted with ether. The ethereal extract was washed with aqueous $NaHCO_3$ and water, dried, and concentrated to furnish the bromide **13** as a pale yellow oil (2.2 g) which was used directly in the next reaction. The bromide dissolved in benzene (5 ml) was added dropwise with shaking to diethyl sodiomalonate [prepared from NaH (0.4 g, 17 mmol) and diethyl malonate (4 g, 25 mmol)] in benzene (25 ml). The mixture was refluxed for 12 h and then cooled, washed with water, and dried. Removal of benzene and excess diethyl malonate left a residue which was evaporatively distilled at 170-172°C (bath temp.)/0.2 mm to furnish the diester **14** as a viscous liquid (2.4 g, 70%); IR (Film): 1745, 1735, 1620, 1605 cm^{-1}. Anal. calcd. for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.92; H, 7.10.

A mixture of **14** (2.2 g), KOH (3g), EtOH (25 ml) and water (5 ml) was refluxed for 4 h. Usual work-up afforded a solid diacid which was decarboxylated by heating it at 200°C for 20 min. The product was crystallised from benzene to furnish **15** (1.25 g, 80%), m.p. 127-128°C; IR (KBr): 1710, 1620, 1595 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.47-3.30 (m, 4H), 2.55 (s, 3H), 3.97 (s, 3H), 6.71 (s, 1H), 7.43-7.67 (m, 2H), 7.93-8.40 (m, 2H), 10.40 (bs, 1H). Anal. calcd. for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found : C, 73.55; H, 6.47.

3,9-Dioxo-4a-methyl-1,2,3,4,4a,9-hexahydrophenanthrene (4) : To a solution of the acid **15** (500 mg, 2 mmol) in CH_2Cl_2 (5 ml) was added oxalyl chloride (760 mg, 6 mmol) and the mixture was refluxed for 4 h. Removal of the solvent and excess oxalyl chloride furnished the acid chloride as a pale yellow liquid (500 mg). The crude acid chloride dissolved in ether (10 ml) was added during 30 min to an ice-cold solution of diazomethane (large excess) in ether and the resulting solution was left at room temperature for 12 h. It was then concentrated to afford the diazoketone **1** as a yellow solid (500 mg) [IR ($CHCl_3$) : 2105, 1640, 1600 cm^{-1}]. The crude diazoketone dissolved in CH_2Cl_2 (10 ml) was added during 3 min to a vigorously stirred solution of trifluoroacetic acid (15 ml) in CH_2Cl_2 (15 ml) at -20°C. The mixture was stirred at -20°C for another 5 min, diluted with CH_2Cl_2 (25 ml), washed with water (3 x 20 ml), and dried. Evaporation of the solvent left a residue which was chromatographed over silica gel (15 g). Elution of the column with ether-light petroleum (1:19) afforded the enedione **4** (240 mg, 52%), m.p. 182°C (from acetone-light petroleum); IR (KBr) : 1708, 1660, 1630, 1598 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.54 (s, 3H), 2.37-3.20 (m, 6H), 6.48 (1H, vinyl proton signal displaying small allylic coupling), 7.23-7.67 (m, 3H), 8.10-8.27 (m, 1H). Anal. calcd. for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found : C, 79.74; H, 6.40.

Methyl 4,7-dimethoxy-1-methyl-2-naphthoate (16) and **Methyl 4,5-dimethoxy-1-methyl-2-naphthoate (17)** : Stobbe condensation of 3-methoxyacetophenone with dimethyl succinate in the presence of sodium hydride[3] afforded the half acid-ester **9** as a viscous liquid in 72% yield. Starting from **9** (5 g, 19 mmol), the steps of cyclisation (Ac_2O, NaOAc), deacetylation (MeOH, p-$MeC_6H_4SO_3H$), and methylation (MeI, K_2CO_3, DME) were carried out as for **11** to furnish an oily product (2.4 g) which was chromatographed on neutral alumina (70 g). Elution of the column with benzene-light petroleum (1:6) afforded the ester **16** (1.53 g, 31% yield from **9**), m.p. 90-91°C (from ether-light

petroleum); IR (KBr): 1715, 1620, 1598 cm^{-1}; ^1H NMR ($CDCl_3$): δ2.75 (s, 3H), 3.93 (s, 3H), 3.96 (s, 3H), 3.98 (s, 3H), 7.02 (s, 1H), 7.22 (d of d, 1H, J = 8,2 Hz), 7.36 (d, 1H, J = 2 Hz), 8.22 (d, 1H, J = 8 Hz). Anal. calcd. for $C_{15}H_{16}O_4$: C, 69.22; H, 6.20. Found : C, 69.31; H, 6.11.

Further elution of the column with benzene-light petroleum (1:1) provided the ester **17** (450 mg, 9% based on **9**), m.p. 75-76°C; IR (KBr): 1715, 1625, 1605 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.77 (s, 3H), 3.94 (s, 3H), 3.95 (s, 3H), 3.98 (s, 3H), 6.93 (d, 1H, J = 8 Hz), 7.14 (s, 1H), 7.44 (d of d, 1H, J = 8,8 Hz), 7.70 (d, 1H, J = 8 Hz). Anal. calcd. for $C_{15}H_{16}O_4$: C, 69.22; H, 6.20. Found : C, 69.03; H, 6.32.

4,7-Dimethoxy-2-hydroxymethyl-1-methylnaphthalene (18) : Reduction of the ester **16** (1.5 g, 5.7 mmol) with $LiAlH_4$ (400 mg, 10.5 mmol) in anhydrous ether (30 ml) furnished the alcohol **18** (1.27 g, 95%), m.p. 96°C (from benzene-light petroleum); ^1H NMR ($CDCl_3$): δ 2.34 (s, 3H), 2.61 (bs, 1H), 3.84 (s, 3H), 3.88 (s, 3H), 4.67 (s, 2H), 6.62 (s, 1H), 7.00 (d of d, 1H, J = 9,2.5 Hz), 7.05 (d, 1H, J = 2.5 Hz), 8.07 (d, 1H, J = 9 Hz). Anal. calcd. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found : C, 72.29; H, 7.15.

3-(4,7-Dimethoxy-1-methyl-2-naphthyl)propanoic acid (21) : Treatment of the primary alcohol **18** (1.2 g, 5.2 mmol) with PBr_3 (540 mg, 2 mmol) in benzene at 50°C for 2 h afforded the bromide **19** (1.28 g) which was directly used in the next step. Reaction of the bromide with diethyl sodiomalonate in benzene as described for **14** provided the diester **20** (1.17 g, 72%), b.p. 185°C (bath temp.)/0.1mm. Anal. calcd. for $C_{21}H_{26}O_6$: C, 67.36; H, 7.00. Found : C, 67.51; H, 7.22.

Hydrolysis of **20** (1.1 g) with 10% methanolic KOH (12 ml) followed by decarboxylation of the resulting diacid afforded the acid **21** (680 mg, 85%), m.p. 149-150°C (from benzene); IR (KBr): 1705, 1622, 1600 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.50-3.33 (m, 4H), 2.53 (s, 3H), 3.98 (s, 6H), 6.58 (s, 1H), 7.14 (d of d, 1H, J

= 9,2.5 Hz), 7.29 (d, 1H, J = 2.5 Hz), 8.23 (d, 1H, J = 9 Hz). Anal. calcd. for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found : C, 69.77; H, 6.81.

3,9-Dioxo-6-methoxy-4a-methyl-1,2,3,4,4a,9-hexahydrophenanthrene (5) : The conversion of the acid **21** (600 mg) into the diazomethyl ketone **2** was carried out as described for **1**. A solution of the crude diazoketone (600 mg) in CH_2Cl_2 (12 ml) was added during 3 min to a stirred solution of TFA (15 ml) in CH_2Cl_2 (15 ml) at -25°C. After the addition, the mixture was stirred at -25°C for 5 min, diluted with CH_2Cl_2 (30 ml), and washed with water. The solvent was dried and evaporated off. The residue was chromatographed on silica gel (20 g). Elution of the column with ether-light petroleum (1:19) afforded the enedione **5** (280 mg, 50%), m.p. 171-172°C (from acetone-light petroleum); IR (KBr): 1710, 1655, 1630, 1598 cm^{-1}; ^1H NMR ($CDCl_3$): δ1.53 (s, 3H), 2.48-3.17 (m, 6H), 3.91 (s, 3H), 6.48 (1H, vinyl proton signal showing small allylic coupling), 6.93 (d, 1H, J = 2 Hz), 7.01 (d of d, 1H, J = 8,2 Hz), 8.22 (d, 1H, J = 8 Hz). Anal. calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found : C, 75.11; H, 6.45.

2-Acetyl-4,7-dimethoxy-1-methylnaphthalene (24) : A mixture of NaH (100 mg, 4 mmol), dimethyl sulphone (380 mg, 4 mmol), and DMSO (3 ml) was stirred at 65°C for 30 min. It was then cooled and a solution of the ester **16** (520 mg, 2 mmol) in THF (4 ml) was added. The resulting mixture was stirred at 65°C for 1 h, cooled, poured into a mixture of ice and dil. HCl, and extracted with chloroform. The organic extract was washed with aqueous $NaHCO_3$ and water, dried, and concentrated to furnish the crude β-ketosulphone **22** as a solid compound (605 mg). This was dissolved in a mixture of AcOH (2 ml) and EtOH (3 ml). Zinc dust (650 mg) was added and the resulting mixture was stirred at 30°C for 2 h. After the insoluble material had been separated and washed with ether, the combined organic solution was washed with aqueous $NaHCO_3$ and water, dried and concentrated.

The solid residue was chromatographed on neutral alumina (15 g). Elution with benzene-light petroleum (1:4) afforded the ketone **24** (370 mg, 75%), m.p. 119-120°C (from methanol); IR (KBr): 1684, 1620, 1600 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.53 (s, 3H), 2.57 (s, 3H), 3.87 (s, 3H), 3.92 (s, 3H), 6.58 (s, 1H), 6.93-7.17 (m, 2H), 8.05 (d of d, 1H, J = 9,1 Hz). Anal. calcd. for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found : C, 73.59; H, 6.85.

Acknowledgement: We are grateful to the CSIR, New Delhi for financial support.

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