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MOLECULAR REARRANGEMENT IN DITERPENES†

AJOY K. BANERJEE
Centro de Química, Instituto Venezolano de Investigaciones Científicas (I.V.I.C.). Apartado 1827, Caracas-101, Venezuela

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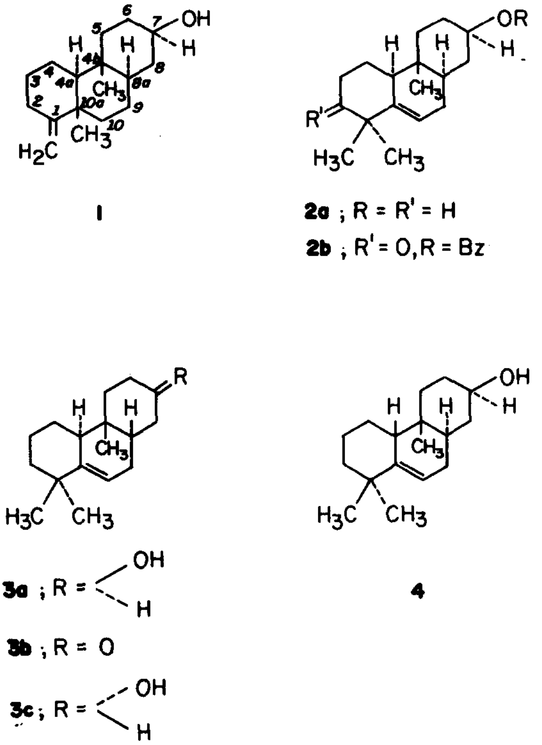
Abstract—The acid catalysed rearrangement of 7β-hydroxy-4bβ-10aβ-dimethyl-1-methylene-*trans-anti,trans*-perhydrophenanthrene 1 has been described.



Scheme 1.

In the continuation of our studies on rosane diterpene[1,2] the synthesis of 7β - hydroxy - 4bβ,10aβ - dimethyl - 1 - methylene - *trans,anti,trans* - perhydrophenanthrene 1 was reported.[3,4] Due to the structural and stereochemical pattern of the phenanthrene 1, it was planned to study its molecular rearrangement in the presence of acid to similar rearrangement of steroids and terpenoids.[5] The acid catalysed rearrangement of the phenanthrene 1 with polyphosphoric acid (PPA) and H_2SO_4 is the topic of the present communication.[6]

The phenanthrene 1 was stirred with PPA in an oil bath (150–170°) for 30 hr. No detectable amount of the phenanthrene 1 remained as detected by tlc analysis. A gummy material was obtained which on chromatographic purification afforded four products (A, B, C and D).

The product A, m.p. 115–116°, showed a molecular ion *m/e* 248 in the MS and IR absorption at 3280 (OH) and 3045 (C=CH) cm^{-1}. In the NMR spectrum it exhibited three sharp singlets at δ 1.01, 1.06 and 1.15 with a total integration corresponding to nine hydrogens indicating three Me groups. The appearance of a broad signal centered at δ 5.56 ppm which corresponded to a single H suggested the presence of olefinic H. Based on these spectroscopic data the structure **2a** was assigned to the product A and this was confirmed by direct comparison (m.p. and IR) with an authentic specimen.[7]

The compound B had a peak at *m/e* 248 in the MS and showed IR absorption at 3048 (C=CH) and 3280 (OH) cm^{-1}. In the NMR spectrum it exhibited three Me groups at δ 1.01, 1.03 and 1.12 and an olefinic H at δ 5.54. Thus two possible structures **3a** and **4**, resulting from the isomerisation of the ring junctures A and B or B and C, could be assigned to the compound B. The compound B on oxidation with CrO_3-3,5-dimethylpyrazole[8] afforded a CO compound (IR spectrum) which on reduction with lithium tri-t-butoxyaluminium hydride $|LiAlH\ (OBu)_3|$ afforded two alcohols, one of which had m.p. 132–133° and the other was noncrystalline. The predominant alcohol, m.p. 132–133°, was identified as **3c** by direct comparison (m.p. and IR) with an authentic specimen.[9] Thus the product B and its oxidation product must possess the structures **3a** and **3b** respectively. The noncrystalline alcohol owing to the poor yield, was not investigated.

The compound C, a colorless liquid, had a molecular ion at *m/e* 248 in the MS and showed absorption at 3045 (C=CH) and 3280 (OH) cm^{-1} in the IR spectrum. Compound C which exhibited three Me groups at δ 1.04, 1.06 and 1.12 and one olefinic proton signal centered at δ 5.42, upon oxidation with CrO_3-3,5-dimethyl pyrazole[8] afforded a CO compound as shown by the sharp CO band at 1710 cm^{-1} in the IR spectrum. The crude ketonic compound on treatment with HCl afforded a low melting α,β-unsaturated ketone as evidenced by the appearance of a molecular ion at *m/e* 246 in the MS and a strong α,β-unsaturated CO band at 1650 cm^{-1} in the IR spectrum. The resulting α,β-unsaturated ketone was completely different from the known α,β-unsaturated ketone **6** (IR and tlc comparison). As in the case of the compound B, there lies also the possibility of isomerisation of the ring junctures of A and B or B and C of the compound C. Thus the compound C and the α,β-unsaturated ketone obtained from C was assigned to the structure **5** and **7** respectively. The configuration at C-8a of the compound **5** and **7** also the configuration at C-4b

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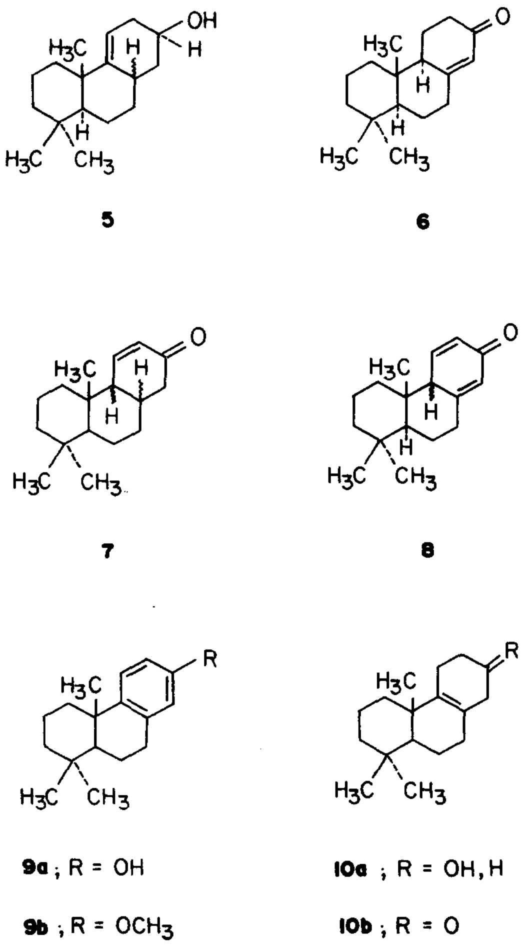
†Dedicated to Prof. K. Takeda on the occasion of his 72nd birthday.

of the compound 7 remained unsettled. In order to confirm the structure of the α,β-unsaturated ketone 7, it was brominated with phenyltrimethyl ammonium perbromide (PTAB). The crude bromo compound obtained as a brown solid was subjected to dehydrobromination[11] with anhyd $CaCO_3$ in refluxing N,N-dimethylacetamide (DMA). A mixture of products, as observed by tlc, was obtained. The crude products had a molecular ion *m/e* 248 in the MS and showed absorption λ_{max} 239 mμ in the UV spectrum. From the NMR analysis of the crude dehydrohalogenated products it was apparent that the crude dehydrohalogenated product contained a mixture of the dienone **8** and its ketonic tautomer. The crude dehydrohalogenated product was subjected to dienone-phenol rearrangement conditions by treating with sulphuric acid. The phenol **9a** obtained in 72% yield showed in the NMR spectrum a singlet at δ 5.90 due to phenolic OH and a multiplet in the region δ 6.41–7.25 corresponding to three aromatic protons. The phenol **9a** on methylation with dimethyl sulfate and alkali afforded **9b**, m.p. 82–83° and this was found to be identical by direct comparison with an authentic specimen.[10]

The compound D, a semi-solid material, lacked an olefinic proton signal in the NMR spectrum and in the IR spectrum absorption at 1620 cm^{-1} and the complete absence of the absorption in the region 3045–3060 cm^{-1} indicated a tetrasubstituted olefinic bond in the compound D. In the MS the compound D had molecular ion at *m/e* 248. Thus two possible structures **10a** and **11a** can be assigned to the compound D. The compound D on oxidation with CrO_3-3,5-dimethylpyrazole[8] afforded a CO compound which on treatment with mineral acid afforded an α,β-unsaturated ketone as shown by the strong absorption at 1650 cm^{-1} in the IR spectrum. The α,β-unsaturated ketone was identified as **6** by comparison (m.p. and IR) with an authentic specimen.[10] Thus the compound D and its oxidation product must possess the structure **10a** and **10b** respectively.


5

6

7

8

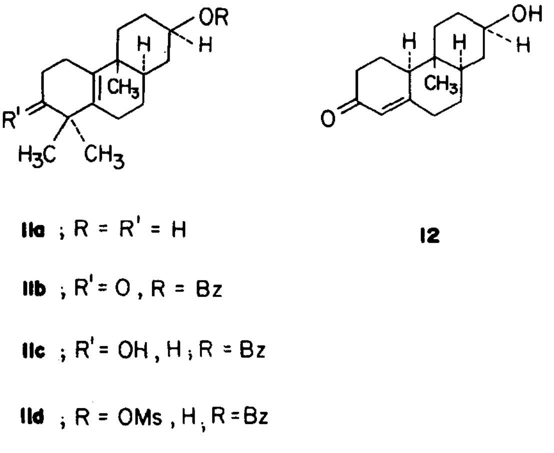
9a ; R = OH

9b ; R = OCH_3

10a ; R = OH, H

10b ; R = O

Scheme 2.


11a ; R = R' = H

11b ; R' = O , R = Bz

11c ; R' = OH , H ; R = Bz

11d ; R = OMs , H , R = Bz

12

Scheme 3.

Next our attention was turned towards the rearrangement study of the phenanthrene **1** with H_2SO_4. The soln of **1** in acetone and H_2SO_4 was kept at room temp. for 60 hr. A reddish black material was obtained which on chromatographic purification afforded a crystalline material in 60% yield and a liquid material in 25% yield. The solid material was identified as **2a** by direct comparison with an authentic specimen.[7] The noncrystalline material showed molecular ion *m/e* 248 in MS and in the NMR spectrum exhibited three Me peaks at δ 1.01, 1.06 and 1.18 but the olefinic proton signal was completely absent. The liquid material decolorized Br_2 in carbon tetrachloride indicating the presence of double bond. In the IR spectrum beside presenting an OH band at 3275 cm^{-1} it showed absorption at 1630 cm^{-1}. As it was completely different from the compound **10a** (IR comparison) the structure **11a** was assigned to it. The confirmation of the structure **11a** was obtained as follows. It was observed[7] that the methylation of the α,β-unsaturated ketone **12** with MeI in the presence of t-BuOK in t-BuOH and benzoylation gave derivative **2b** in excellent yield when the α,β-unsaturated ketone **12** and the base were allowed to remain in contact for a short time prior to the addition of the MeI. When the α,β-unsaturated ketone **12** was kept for a longer period in contact with the base, a significant amount of the $\Delta^{4a,10a}$ **11b** was formed as evidenced by the lower integration the C-10 proton signal in the NMR spectrum. On separation, the derivative **11b** exhibited complete absence of olefinic proton in the NMR spectrum and a molecular ion *m/e* 366 in the MS. The compound **11b** on reduction with $NaBH_4$ afforded a mixture of alcohols **11c** as observed by two overlapping spots in tlc. The alcohol **11c** was converted to the noncrystalline mesyl derivative **11d** which on reduction[12] with NaI/Zn followed by alkaline hydrolysis afforded a product which was identical with **11a** (IR and tlc). Thus the structure of **11a** was established for the liquid product. The other products obtained by the sulphuric acid treatment of phenanthrene

1 were impure and produced in negligible quantity. Thus the structures of these products could not be determined.

EXPERIMENTAL

M.ps were determined on a Kofler hot-stage and are uncorrected. Unless otherwise specified, IR spectra were taken on a Perkin–Elmer 337 spectrometer for KBr discs or liquid films and UV spectra were measured with a Cary model 15 spectrometer. NMR spectra were obtained with a Varian A-60 spectrometer. Chemical shifts are reported as δ units using TMS as an internal standard. Mass spectra were recorded on a Hitachi Perkin–Elmer RMU 6E at 70 eV using a direct inlet system. Merck standard alumina activity II–III was used for column chromatography. For tlc, Merck silica gel G was used and the spots were identified by exposure to I_2 vapour. All organic extracts were dried over anhydrous $MgSO_4$ and evaporated under reduced pressure below 40°. Microanalyses were carried out in Microanalytical Laboratory, 5251 Elbach über Engelskirchen, West Germany. All compounds reported here are racemic.

PPA catalysed rearrangement of 7β - hydroxy - 4bβ,10aβ - dimethyl - 1 - methylene - trans,anti,trans *- perhydrophenanthrene* 1

A mixture of 1 (0.56 g) and PPA [from P_2O_5 (12 g) and H_3PO_4 (10 ml)] was heated on oil bath (150–170°) for 30 hr. The progress of the reaction was monitored by tlc (C_6H_6:ether 1:1). The mixture was then decomposed with crushed ice and then extracted with ether. On removal of the solvent a dense material was obtained which on chromatographic purification over silica gel afforded the following fractions:

(i) *Benzene*:*ether* (1:1) eluted **2a** (0.25 g; 44.6%) which on crystallisation from MeOH had m.p. 114–116°, m.m.p. 116–117° (lit.[6] 116–118°).

(ii) *Benzene*:*ether* (45:35) afforded **3a** (48 mg; 8.5%), homogeneous in tlc, b.p. 160–170°/0.5 mmHg (bath), *m/e* 248 (M^+); IR (film) 3280 (OH), 3045 (C=CH) and 1635 (C=C) cm^{-1}, NMR ($CDCl_3$) δ 1.01 (3H, s), 1.03 (3H, s) and 1.12 (3H, s) (1,1-Me and 4b-Me) and 5.54 (1H, t, H-10). (Calc. for $C_{17}H_{28}O$: C, 82.20; H, 11.26. Found: C, 82.09; H, 11.31%).

(iii) *Benzene*:*ether* (35:65) eluted **5** (0.11 g; 19.6%), b.p. 155–158°/0.3 mmHg (bath), *m/e* 248 (M^+) and 230 (M^+-H_2O); IR (film) 3280 (OH), 3045 and 1630 (C=CH) cm^{-1}; NMR ($CDCl_3$) δ 1.04 (3H, s), 1.06 (3H, s), 1.16 (3H, s) (1,1-CH_3 and 4a-CH_3) and 5.42 (1H, m, 10-H). (Calc. for $C_{17}H_{28}O$: C, 82.20; H, 11.36. Found: C, 82.04; H, 11.32%).

(iv) *Benzene*:*ether* (30:70) eluted the **10a** (55 mg; 9.8%) which was a semi-solid material; *m/e* 248 (M^+), IR (film) 3270 (OH) and 1620 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 1.02 (3H, s), 1.08 (3H, s), 1.16 (3H, s) (1,1-Me and 4a-Me). (Calc. for $C_{17}H_{28}O$: C, 82.20; H, 11.36. Found: C, 82.08; H, 11.31%).

Oxidation of the olefin 3a

3,5-Dimethylpyrazole (50 mg) was added to a suspension of CrO_3 (60 mg) in CH_2Cl_2 (10 ml) and the mixture was stirred at room temp. under argon for 15 min. To the resulting soln **3a** (48 mg) in CH_2Cl_2 (1 ml) was added in one portion and the mixture was stirred at room temp. for 20 min. The solvent was removed under reduced pressure and the residue was extracted several times with ether. The combined organic extract was washed with brine and dried. On removal of the solvent followed by filtering over a short column of alumina, **3b** (42 mg, 85%) was obtained as pale yellow oil; *m/e* 246 (M^+); IR (film) 1710 (C=O) cm^{-1}. (Calc. for $C_{17}H_{26}O$: C, 82.87; H, 10.64. Found: C, 82.64; H, 10.60%).

Reduction of the ketone 3b

A soln of **3a** (40 mg) in THF (25 ml) was slowly added to a stirred suspension of $LiAlH(OBu)_3$ (30 mg) in THF (20 ml) cooled to 0°. The mixture was stirred for 8 hr at 0° and then a soln (20 ml) of ammonium sulfate (80%) was added dropwise in 10–15 min with vigorous stirring and cooling below 0° (vigorous evolution of H_2). The evaporation of the dried organic extract afforded a gummy material which was chromatographed over alumina. Elution with benzene:ether (40:60) afforded **3c** (28 mg; 58.3%) which on crystallisation from ether–hexane melted at 132–133°, m.m.p. 132–133° (lit.[9] 132–134°). Further elution with benzene:ether (38:62) afforded a noncrystalline material (8 mg) which was not investigated.

1,2,3,4,4a,9,10,10a *- Octahydro - 7 - methoxy - 1,1,4aβ - trimethylphenanthrene* 7b

To a suspension of CrO_3 (80 mg) in CH_2Cl_2 (25 ml) was added 3,5-dimethylpyrazole (80 mg) and the mixture was stirred at room temp. under argon for 15 min. To the resulting dark red soln, **5** (90 mg) was added in one portion and the mixture was stirred at room temp. for 25 min. The solvent was removed under reduced pressure and the residue was extracted several times with ether. The combined extract was washed with brine, and dried. On removal of the solvent, a reddish liquid was obtained which on filtering over a short column of alumina afforded a colourless viscous liquid (72 mg); IR (film) 1710 (C=O) cm^{-1}. To the crude product (72 mg) in acetone (25 ml) was added HCl (10%, 10 ml) and the mixture was stirred at room temp for 18 hr. The usual work-up followed by purification over a column of alumina afforded the noncrystalline **7** (70 mg; 97.2%); *m/e* 246 (M^+); IR (film) 1660 (C=C–C=O) cm^{-1}. The ketone **7** was found to be unstable as it turned deep yellow and then green in contact with air.

To a soln of **7** (70 mg) in distilled THF (15 ml) cooled to 0°, was added PTAB (0.11 g; m.p. 114–115°, BDH supplier). After 1 hr stirring, another lot of PTAB (10 mg) was added and the mixture was stirred for a further 10 min. The mixture was poured into an ice-cold soln of $NaHCO_3$ (5%, 10 ml) followed by the addition of $Na_2S_2O_3$ (0.1 N, 10 ml). The soln was extracted with ether, washed with brine and then dried. On removal of the solvent a viscous liquid was obtained; on trituration with cold MeOH on a pale yellow bromo compound (90 mg), m.p. 78–82° was obtained. The bromo compound without putification was dissolved in DMA (60 ml) and to it was added $CaCO_3$ (5 g). The mixture was heated under reflux for 40 min. The mixture was cooled and then filtered. The filtrate was extracted thoroughly with ether several times. The combined extract was washed with a sat $NaHCO_3$ aq, water and then dried. On removal of the solvent a semi-solid material (62 mg) was obtained which without purification was dissolved in MeOH (10 ml) containing water (2 ml) and H_2SO_4 (1 ml). The mixture was heated under reflux for 4 hr, cooled and then diluted with water. The mixture was extracted with ether, washed with brine and then dried. Removal of the solvent followed by purification over alumina afforded the oily **9a** (45 mg); *m/e* 244 (M^+); IR (film) 3640 (OH) cm^{-1}, NMR ($CDCl_3$) δ 1.02 (3H, s), 1.08 (3H, s), 1.12 (3H, s) (1,1-Me and 4a-Me), 5.90 (1H, s, phenolic OH) and 6.41–7.25 (3H, m, aromatic).

The phenol **9a** (40 mg) was methylated with Me_2SO_4 (2 ml), K_2CO_3 (0.8 g) and Me_2CO (25 ml) under reflux for 24 hr. The filtrate of the mixture was evaporated and extracted with ether after water was added. The extract was washed with brine, dried, and then evaporated to obtain **9b** (42 mg, 93%) which on crystallisation with EtOH melted at 84–85°, m.m.p. 83–84° (lit.[9] 85–86°).

Oxidation of 10a *and isomerisation of* 10b

3,5-Dimethylpyrazole (60 mg) was added to a suspension of CrO_3 (80 mg) in CH_2Cl_2 (10 ml) and the mixture was stirred at room temp. under argon for 15 min. To the resulting soln **10a** (50 mg) in CH_2Cl_2 (2 ml) was added in one portion and the mixture was stirred at room temp. for 20 min. The solvent was removed under reduced pressure and the residue was extracted several times with ether. The combined organic extract was washed with brine and dried. On removal of the solvent followed by filtering the residue over a short column of alumina was obtained the oily **10b** (45 mg; 91%); *m/e* 246 (M^+); IR (film) 1715 (C=O) cm^{-1}.

The crude **10b** (45 mg) in Me_2CO (15 ml) was treated with 3N HCl (5 ml) with stirring at room temp. for 10 hr. The soln was diluted with water and extracted with ether. The organic extract was washed with brine and evaporated to give **6** (42 mg; 93%) which on crystallisation from pet. ether (60–80°) had m.p. 92–94°, m.m.p. 92–93° (lit.[9] 92.5–93.5°).

H_2SO_4 *Rearrangement of the phenanthrene* 1

To 1 (0.51 g) in Me_2CO (25 ml) was added ice-cold conc H_2SO_4 (20 ml) and the soln was stirred at room temp. for 60 hr. The soln turned deep yellow and then red. It was poured carefully on crushed ice, diluted with water and then extracted with ether. The ether extract was washed with brine, dried and concentrated to obtain a deep red material which was chromatographed over silica gel. Elution with benzene:ether (1:1) afforded **2a** (0.31 g; 60%), m.p. 115–116°, m.m.p. 115–116° (lit.[6] 116–118°). Further elution with benzene:ether (55:45) afforded **11a** (0.12 g; 25%), a dense liquid which failed to crystallise; *m/e* 248 (M^+) and 230 (M^+-H_2O); IR (film) 3275 (OH) and 1630 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 1.01 (3H, s), 1.06 (3H, s) and 1.18 (3H, s) (1,1-Me and 4b-Me). (Calc. for $C_{17}H_{28}O$: C, 82.20; H, 11.36. Found: 82.08; H, 11.32%).

7β - *Benzoyloxy* - 1,2,3,4,4b,5,6,7,8,8a,9,10 - *dodecahydro* - 2 - *oxo* - 1,1,4bβ - *trimethylphenanthrene* 11b

A soln of 12 (1 g) in dry benzene (40 ml) was added to a soln of BuOK (2 g) in BuOH (20 ml) and the mixture was stirred at room temp. for 10 min. To this MeI (4.2 g) was added very slowly (2 hr). The mixture was diluted with water and extracted with ether. The organic extract was washed, dried and evaporated to a brown solid (1.03) which without purification was dissolved in dry pyridine (15 ml) and to it was added benzoyl chloride (3 ml). The usual work-up afforded a yellowish white solid which on elution with benzene:hexane (6:4) over alumina afforded **2b** (0.62 g; 40%) and this on crystallisation from ether–hexane had m.p. 178–180°, m.m.p. 178–179° (lit.[6] 179–181°). Further elution (benzene:hexane 8:2) afforded **11b** (0.28 g; 18.3%), a dense liquid, homogeneous in tlc, *m/e* 366 (M^+) and 244 (M^+-C_6H_5 COOH); IR (film) 1705 (unresolved ketonic and ester CO) and 1275 (benzoate O–C) cm^{-1}; NMR ($CDCl_3$) δ 1.02 (3H, s), 1.06 (3H, s), 1.17 (3H, s) (1,1-Me and 4b-Me), 4.95 (1H, m) (7-H) and 7.25–8.25 (5H, m) (benzenoid H). (Calc. for $C_{24}H_{30}O_3$: C, 78.65; H, 8.25. Found: C, 78.61; H, 8.36%).

7β - *Hydroxy* - 1,2,3,4,4b,5,6,7,8,8a,9,10 - *dodecahydro* - 1,1,4bβ - trimethylphenanthrene 11a

The phenanthrene **11b** (0.2 g) dissolved in MeOH (20 ml) was treated with $NaBH_4$ (0.1 g) and stirred for 5 hr at 10°. The usual work-up afforded **11c** (0.16 g); m.p. 118–125°; *m/e* 368 (M^+), which was dissolved in pyridine (12 ml) and treated with methanesulphonyl chloride (0.11 g) at room temp. overnight. The usual work-up afforded noncrystalline **11d** (0.13 g) which without purification was dissolved in glyme (5 ml) and to it was added NaI (0.18 g) and Zn powder (0.14 g). The mixture was heated under reflux for 3 hr. The mixture was filtered to remove excess NaI and Zn powder. The filtrate was poured into water and extracted with ether. The organic extract was washed with brine, dried, and concentrated. The residual semi-solid material dissolved in MeOH (30 ml) was treated with a soln of 10% NaOH (8 ml) and heated under reflux for 6 hr. The usual work-up followed by purification over alumina afforded **11a** (0.11 g, 75%).

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