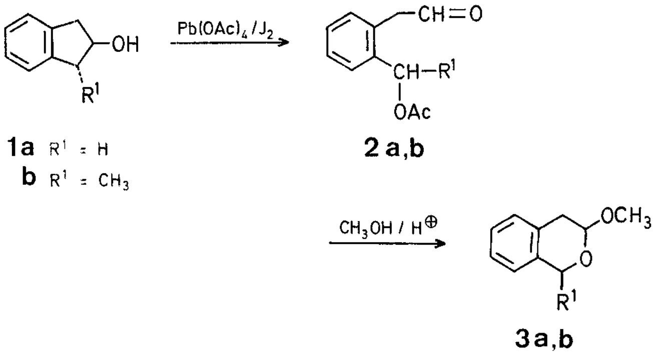
A Novel Route for the Synthesis of 3,4-Dihydro-1*H*-2-benzopyrans and 1,3,4,5-Tetrahydro-2-benzoxepins

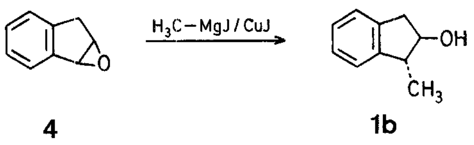
D. G. Talekar, A. S. Rao*

National Chemical Laboratory, Pune-411 008, India

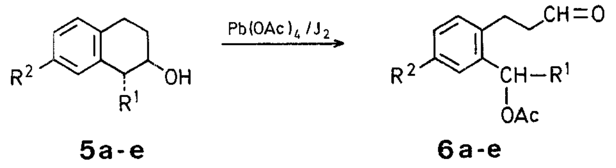
Several 3,4-dihydro-1*H*-2-benzopyrans[1-4] have been found to occur in nature; some of the pyranoquinones[5] such as nanaomycins exhibit interesting biological properties. A number of publications dealing with the synthesis of 3,4-dihydro-1*H*-2-benzopyrans[6-9] and preparation of 1,3,4,5-tetrahydro-2-benzoxepins[10] and their applications have appeared in literature. Since it is known that δ-hydroxy aldehydes cyclize readily to pyrans[11] and ε-hydroxy aldehydes cyclise to oxepins[11], we decided to synthesise the δ-acetoxy aldehyde **2a** from **1a** involving a fragmentation reaction and transform the aldehyde **2a** to the benzopyran **3a**. This route has also been found to be applicable for the synthesis of benzoxepins (**7a-e**).

2,3-Dihydro-1*H*-inden-2-ol (**1a**) furnished the aldehyde **2a** on heating with lead(IV) acetate/iodine[12,13] in benzene. Heating the aldehyde **2a** with methanol in the presence of sulphuric acid gave the benzopyran **3a**. Fragmentation of **1b** furnished the aldehyde **2b**.

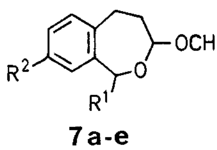




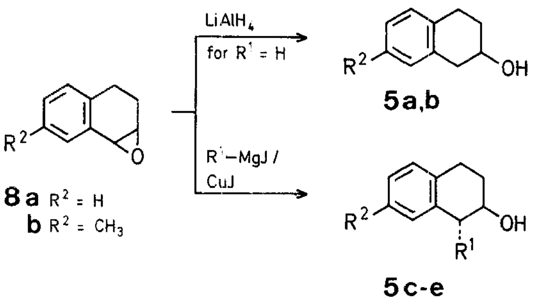
Fragmentation of tetralols **5a-e** proceeded smoothly in the presence of lead(IV) acetate/iodine to furnish the aldehydes **6a-e**. The aldehydes **6a-e** were transformed to the benzoxepins **7a-e** when heated with methanol in the presence of sulphuric acid. The methyl ether **3b** was obtained as a mixture of *cis*- and *trans*-isomers as shown by the N.M.R. spectrum (separate singlets for OCH_3 of *cis* and *trans* isomers) and G.L.C. The methyl ethers **7c-e** were also obtained as mixtures of *cis* and *trans*-isomers.



5,6,7	R¹	R²
a	H	H
b	H	CH₃
c	CH₃	H
d	CH₃	CH₃
e	C₂H₅	H



The tetralols **5a, b** were prepared from **8a, b**. It has been shown recently[14] that oxiranes can be cleaved readily with Grignard reagents in the presence of copper iodide. This reaction has been utilised for the preparation of alcohols **5c–e**.



2-Hydroxy-7-methyl-1,2,3,4-tetrahydronaphthalene (5b); Typical Procedure:

1,2-Epoxy-7-methyl-1,2,3,4-tetrahydronaphthalene[17] (**8b**; 1.6 g, 10 mmol) is added slowly to a stirred solution of lithium aluminium hydride (0.38 g, 10 mmol) in ether (100 ml) at 0 °C. After the addition is complete the solution is allowed to attain room temperature and is further stirred for 2 h. The excess lithium aluminium hydride is destroyed by addition of acetone, ether, and water at 0 °C. The ether layer is then separated and the aqueous layer shaken with ether (3 × 25 ml). The combined ether extracts are washed with water (25 ml), brine (25 ml), and evaporated. The solid residue obtained is crystallised from petroleum ether/benzene to give **5b** as an analytically pure product; yield: 1.2 g (74%); m.p. 84–85 °C.

$C_{11}H_{14}O$	calc.	C 81.44	H 8.70
(162.2)	found	81.13	8.77

I.R. (Nujol): $\nu = 3450$ cm^{-1} (OH).

^{1}H-N.M.R. (CCl$_4$): $\delta = 1.8$ (m, 2H, $Ar{-}CH_2{-}C\underline{H}_2{-}$); 2.23 (s, 3H, $Ar{-}C\underline{H}_3$); 2.8 (m, 4H, $Ar{-}C\underline{H}_2$); 3.9 (m, 1H, $C\underline{H}{-}OH$); 6.7 ppm (s, 3H$_{arom}$).

trans-1,7-Dimethyl-2-hydroxy-1,2,3,4-tetrahydronaphthalene (5d); Typical Procedure:

To a stirred suspension of copper iodide (0.342 g, 1.8 mmol) in tetrahydrofuran (15 ml) is added slowly methylmagnesium iodide (33 mmol) at −30 °C. After 10 min, 1,2-epoxy-7-methyl-1,2,3,4-tetrahydronaphthalene (**8b**; 1.8 g, 11 mmol) is added. The solution is allowed to attain 0 °C and maintained at this temperature for 4 h. Excess of reagent is destroyed with saturated ammonium chloride solution at 0 °C. The ether layer is then separated, the aqueous layer is extracted with ether (4 × 25 ml). The combined ether extracts are washed with water (20 ml), brine (20 ml), and evaporated. The residue is chromatographed over alumina (Grade II). Elution with petroleum ether/ethyl acetate (93 : 7) gives **5d**; yield: 1.21 g (62%); m.p. 69–70 °C.

$C_{12}H_{16}O$	calc.	C 81.77	H 9.15
(176.3)	found	81.95	9.30

I.R. (Nujol): $\nu = 3450$ cm^{-1} (OH).

^{1}H-N.M.R. (CCl$_4$): $\delta = 1.27$ (d, 3H, $J = 7$ Hz, $C\underline{H}_3{-}CH$); 1.8 (m, 2H, $Ar{-}CH_2{-}C\underline{H}_2$); 2.23 (s, 3H, $Ar{-}C\underline{H}_3$); 2.7 (m, 3H, $Ar{-}C\underline{H}_2$; $Ar{-}C\underline{H}{-}$); 3.6 (m, 1H, $C\underline{H}{-}OH$); 6.73 ppm (s, 3H).

3-(2-Acetoxymethylphenyl)-propanal (6a):

A mixture of 2-hydroxy-1,2,3,4-tetrahydronaphthalene (**5a**; 0.4 g, 2.7 mmol), lead(IV) acetate (3.1 g, 7 mmol), iodine (0.686 g, 2.7 mmol), and benzene (30 ml) is heated under reflux for 2 h. Excess lead(IV) acetate is destroyed with ethylene glycol. The benzene layer is washed with sodium thiosulphate solution (3 × 10 ml), water (10 ml), brine (10 ml), and evaporated. The residue is distilled under vacuum to furnish **6a**; yield: 0.45 g (81%); b.p. 145–150 °C/0.1 torr.

$C_{12}H_{14}O_3$	calc.	C 69.88	H 6.84
(206.2)	found	69.73	6.68

I.R. (Neat): $\nu = 1740$ (C=O); 2780 cm^{-1} (aldehyde C—H).

^{1}H-N.M.R. (CCl$_4$): $\delta = 2.07$ (s, 3H, $C\underline{H}_3CO{-}$); 2.9 (m, 4H, $Ar{-}C\underline{H}_2{-}C\underline{H}_2{-}CHO$); 5.20 (s, 2H, $Ar{-}C\underline{H}_2{-}$); 7.20 (s, 4H$_{arom}$); 9.90 ppm (t, 1H, $J = 1$ Hz, $-C\underline{H}O$).

Table. Compounds Prepared

Product	Starting Material	Yield[b] [%]	m.p. [°C] or b.p. [°C]/torr[a]	Molecular Formula[c] or Lit. m.p. or b.p. [°C]/torr
1a	**4**[15]	71	68–69°	69°[16]
1b	**4**[15]	53	150–155°/20	$C_{10}H_{12}O$ (148.2)
2a	**1a**	60	130–135°/0.1	$C_{11}H_{12}O_3$ (192.2)
2b	**1b**	70	130°/0.2	$C_{12}H_{14}O_3$ (206.2)
3a	**2a**	32	165–170°/40	$C_{10}H_{12}O_2$ (164.2)
3b	**2b**	41	155–160°/30	$C_{11}H_{14}O_2$ (178.2)
5a	**8a**[17]	68	145–150°/10	159–161°/26[18]
5b	**8b**	74	84–85°	$C_{11}H_{14}O$ (162.2)
5c	**8a**	58	150–155°/7	$C_{11}H_{14}O$ (162.2)
5d	**8b**	62	69–70°	$C_{12}H_{16}O$ (176.3)
5e	**8a**	53	155–160°/4	$C_{12}H_{16}O$ (176.3)
6a	**5a**	81	145–150°/0.1	$C_{12}H_{14}O_3$ (206.2)
6b	**5b**	79	145–150°/0.05	$C_{13}H_{16}O_3$ (220.3)
6c	**5c**	89	135–140°/0.15	$C_{13}H_{16}O_3$ (220.3)
6d	**5d**	90	135–140°/0.15	$C_{14}H_{18}O_3$ (234.3)
6e	**5e**	85	135–140°/0.13	$C_{14}H_{18}O_2$ (234.3)
7a	**6a**	54	175–180°/25	$C_{11}H_{14}O_2$ (178.2)
7b	**6b**	58	175–180°/25	$C_{12}H_{16}O_2$ (192.3)
7c	**6c**	70	165–170°/20	$C_{12}H_{16}O_2$ (192.3)
7d	**6d**	66	170–175°/20	$C_{13}H_{18}O_2$ (206.2)
7e	**6e**	76	150–155°/6	$C_{13}H_{18}O_2$ (206.2)

[a] Not corrected; for b.p. bath temperature is given.

[b] Yield of pure product isolated by chromatography or distillation.

[c] Satisfactory microanalyses obtained: C ±0.40, H ±0.27.

3-Methoxy-1,3,4,5-tetrahydro-2-benzoxepin (7a):

A mixture of 3-(2-acetoxymethylphenyl)-propanal (**6a**; 0.690 g, 3.3 mmol), methanol (15 ml), and sulphuric acid (0.3 g) is heated under reflux for 2 h. The solution is then diluted with water (20 ml) and extracted with ether (3 × 50 ml). The ether layer is washed successively with water (25 ml), saturated sodium hydrogen carbonate solution (25 ml), again with water (20 ml), and evaporated. The residue is distilled over sodium under vacuum to furnish **7a**; yield: 0.322 g (54%); b.p. 175–180 °C/25 torr.

$C_{11}H_{14}O_2$	calc.	C 74.13	H 7.92
(178.2)	found	74.00	7.73

^{1}H-N.M.R. (CCl$_4$): $\delta = 1.9$ (m, 2H, $Ar{-}CH_2{-}C\underline{H}_2{-}$); 2.8 (m, 2H, $Ar{-}C\underline{H}_2$); 3.40 (s, 3H, $OC\underline{H}_3$); 4.6 (AB type quartet, 2H, $J_{AB} = 14$ Hz, $\delta_{AB} = 0.9$, $Ar{-}C\underline{H}_2{-}O{-}$); 4.67 (t, 1H, $J = 4$ Hz, $O{-}C\underline{H}{-}OCH_3$); 7.0 ppm (s, 4H$_{arom}$).

1,2-Epoxy-7-methyl-1,2,3,4-tetrahydronaphthalene (8b):

6-Methyl-1,2-dihydronaphthalene (1.9 g, 13.2 mol) is transformed to the corresponding bromohydrin according to Ref.[17]; yield: 3.0 g (94%); m.p. 95–96 °C (from petroleum ether/ether).

$C_{11}H_{13}BrO$	calc.	C 54.79	H 5.43
(241.1)	found	54.74	5.55

The bromohydrin (2.8 g, 11.6 mol) on treatment with potassium hydroxide (1.01 g, 18 mmol) dissolved in water (25 ml), is converted to the epoxide **8b**; yield: 1.6 g (90%); m.p. 72–73 °C (from petroleum ether/benzene).

$C_{11}H_{12}O$	calc.	C 82.46	H 7.55
(160.2)	found	82.57	7.44

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