Synthetic and Stereochemical Studies of the Octahydro-1-benzopyran System

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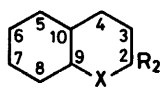
The *cis* and *trans* isomers of the octahydro-1-benzopyran system have been synthesised and their conformations studied by low-temperature ^{13}C and highfield ^{1}H n.m.r. spectroscopy. The position of the conformational equilibrium in the *cis* isomer at −70 °C in $CDCl_3$–$CFCl_3$ (50:50) has been determined as approximately 99.5:0.5 (ΔG^0 −8.9 kJ mol^{-1}) in favour of the conformation having the oxygen axially disposed towards the cyclohexane ring.

Although the octahydro-1-benzopyran system (**1**; R = H, X = O) has been known for many years[1] the stereochemical aspects of this system have been little studied. Indeed, at the commencement of our study there were no reports of the isolation of the *cis* isomer (**2**; R = H, X = O) although the formation of some *trans*-octahydro-1-benzopyran (**3**; R = H, X = O) had been observed during the reductive demercuration of the product formed by the intramolecular oxymercuration of *trans*-2-allylcyclohexanol.[2] The methyl-substituted derivatives of the octahydro-1-benzopyran system have also been little studied although the ^{1}H n.m.r. spectra of the *cis* and *trans* isomers of the 10-methyl-substituted system and a number of its oxo-substituted derivatives have been reported.[3] In contrast the corresponding nitrogen system, decahydroquinoline (**1**; R = H, X = NH),[4,5] and its methyl-substituted derivatives[6,7] have been extensively studied from a stereochemical point of view as has the analogous sulphur system, 1-thiadecalin (**1**; R = H, X = S).[8]



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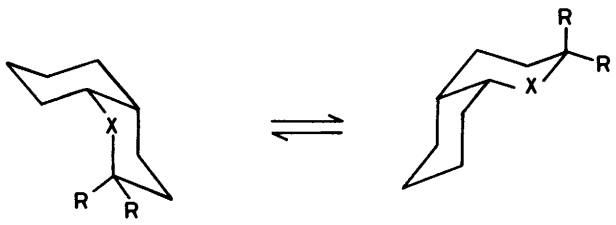

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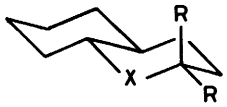

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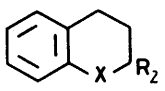
Our initial approach to the synthesis of the *cis* and *trans* isomers of the octahydro-1-benzopyran system and a number of methyl-substituted derivatives was based on the use of the appropriately substituted 2*H*-1-benzopyran-2-ones. These were first converted into the corresponding 2,3-dihydro-2*H*-1-benzopyrans which in turn were reduced to the desired octahydro-1-benzopyran systems.

Interestingly, while the catalytic hydrogenation of quinoline and 1,2,3,4-tetrahydroquinoline in cyclohexane had been found to give predominantly *trans*-decahydroquinoline (**3**; R = H, X = NH),[4] the reduction of the oxygen system, 2,3-dihydro-2*H*-1-benzopyran (**4**; R = H, X = O), gave largely the *cis* isomer of octahydro-1-benzopyran (91%), although a little *trans* isomer was also formed. This suggested that the reduction of the 2,3-dihydro-2*H*-1-benzopyran might be proceeding *via* the enol ether (**5**; R = H, X = O), a view supported by the observation that the hydrogenation of the enol ether (**5**; R = H, X = O) gave this same proportion of *cis*-octahydro-1-benzopyran. However, attempts to detect the formation of the enol ether (**5**; R = H, X = O) during the catalytic hydrogenation of 2,3-dihydro-2*H*-1-benzopyran were inconclusive, suggesting that if the enol ether was formed it was being readily reduced under the conditions needed for its formation.



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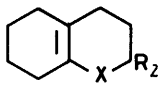

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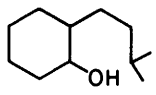

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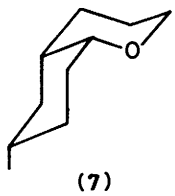

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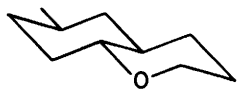

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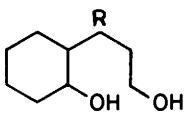

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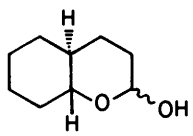

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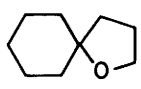


(11)

To obtain further evidence for the proposed reduction route we therefore investigated the catalytic hydrogenation of the dimethyl-substituted system (**4**; R = Me, X = O). A consideration of molecular models suggested that while the presence of the additional methyl groups would have little effect on the ease of formation of the proposed enol ether (**5**; R = Me, X = O) they might significantly reduce the rate of hydrogenation of the proposed intermediate (**5**; R = Me, X = O) by increasing the

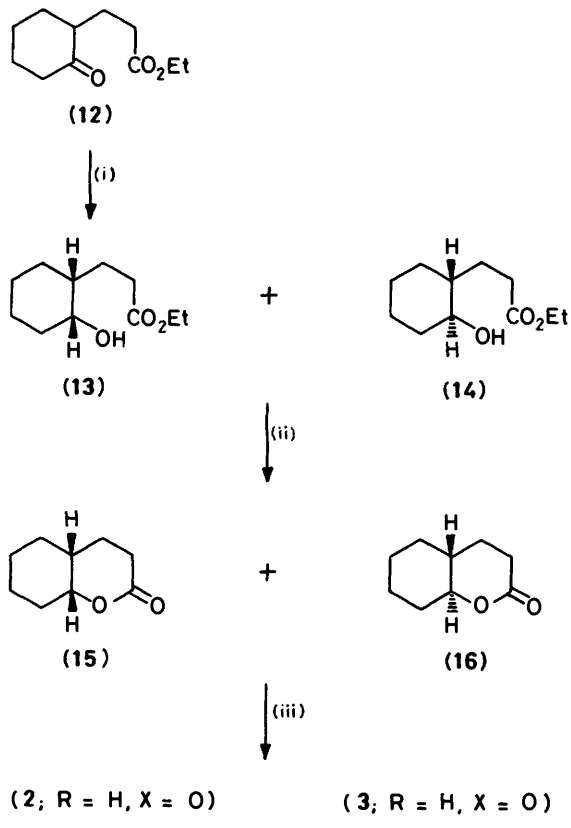
strain in the fully reduced system (**1**; R = Me, X = O) relative to the unsubstituted system (**1**; R = H, X = O).

The initial hydrogenation of the dihydrobenzopyran (**4**; R = Me, X = O) in cyclohexane was allowed to continue until the reduction was complete. As expected, ^{13}C n.m.r. spectroscopy showed the octahydro-2,2-dimethyl-1-benzopyran system (**1**; R = Me, X = O) to be the major product with the *cis* isomer again being predominant (78%). However, a second component was also formed which was shown to be a mixture of the *cis* (33%) and *trans* (67%) isomers of the ring-cleaved product, 2-(3-methylbutyl)cyclohexanol (**6**). The formation of significant quantities of this ring-cleaved product probably reflects the increased strain in the bicyclic system (**1**; R = Me, X = O) arising from the axially disposed methyl substituent since no products arising from ring cleavage were observed in the catalytic hydrogenation of the unsubstituted system (**4**; R = H, X = O). The catalytic hydrogenation of (**4**; R = Me, X = O) was then repeated but stopped before reduction was complete. On this occasion an additional component was observed in the ^{13}C n.m.r. spectrum of the reaction product which was identified as the proposed hydrogenation intermediate 3,4,5,6,7,8-hexahydro-2,2-dimethyl-2*H*-1-benzopyran (**5**; R = Me, X = O). This was confirmed by preparing a sample of (**5**; R = Me, X = O) by reducing the dihydrobenzopyran (**4**; R = Me, X = O) with lithium in a mixture of dimethylamine and ethylamine. The presence of the enol ether (**5**; R = Me, X = O) in the hydrogenation mixture is consistent with our prediction and supports our view that the catalytic hydrogenation of the dihydrobenzopyrans (**4**; R = Me or H, X = O) proceeds predominantly *via* the enol ethers (**5**; R = Me or H, X = O) in which the double bond adopts the bridgehead position.

This reduction pathway, leading to the preferential formation of the *cis*-fused isomers, also appears to occur in other 2,3-dihydro-2*H*-1-benzyopyrans. Thus, for example, the octahydro-6-methyl-1-benzopyran isolated from the catalytic hydrogenation of 2,3-dihydro-6-methyl-2*H*-1-benzopyran was shown to be a mixture of *cis*-6,10-*cis*-9,10-octahydro-6-methyl-1-benzopyran (**7**) (90%) and *cis*-6,10-*trans*-9,10-octahydro-6-methyl-1-benzopyran (**8**) (10%). It is interesting to note that the *cis*:*trans* ratio in this case is essentially the same as that produced in the unsubstituted parent system. Unfortunately, however, we were unable to separate the *cis* and *trans* isomers of those octahydro-1-benzopyran systems we had prepared and it was therefore clear that an alternative approach would be needed to prepare pure samples of the *cis* and *trans* isomers of the parent system and its methyl-substituted derivatives. The route developed for the parent system is shown in the Scheme.

In this route the reduction of 2-[2-(ethoxycarbonyl)ethyl]-cyclohexanone (**12**) was carried out using catalytic hydrogenation rather than sodium borohydride since the latter led to the formation of approximately equal quantities of the *cis* and *trans* isomers of the diol (**9**; R = H). This reduction of the ester group has also been observed in the corresponding methyl ester[9] and has been attributed to the possible formation of the lactones (**15**) and (**16**) by the cyclisation of the initially formed cyclohexanols (**13**) and (**14**). Diol formation has been shown to result from reduction of the lactones (**15**) and (**16**) with sodium borohydride.[9]

Catalytic hydrogenation of the cyclohexanone (**12**) led to the formation of approximately equal quantities of the *cis*- and *trans*-cyclohexanols (**13**) and (**14**). Although these cyclohexanols were observed to cyclise readily in the presence of either acid or base, the resulting lactones (**15**) and (**16**) could not be readily separated. Separation of the cyclohexanols (**13**) and (**14**) was therefore carried out immediately after their formation before any cyclisation could occur. The pure cyclohexanols were then cyclised to give the corresponding isomerically pure lactones.



Scheme. *Reagents:* (i) H_2/Pd(C). (ii) H^+(−EtOH). (iii) BH_3·Me_2S

Although the hydrogenation of an isomeric mixture of the lactones (**15**) and (**16**) to give octahydro-1-benzopyran has been reported,[10] using a platinum oxide catalyst in glacial acetic acid containing a precisely regulated amount of perchloric acid, we were unsuccessful in applying this approach. However, following reports[11] that certain δ-lactones can be reduced to give ethers using a mixture of lithium aluminium hydride and boron trifluoride–diethyl ether, we investigated the use of the borane–dimethyl sulphide complex for the reduction of the lactones (**15**) and (**16**). An initial attempt to reduce the *trans*-lactone (**16**) using a freshly opened sample of the borane–dimethyl sulphide complex was successful and gave the desired *trans*-octahydro-1-benzopyran system (**3**; R = H, X = O) in excellent yield. However, in a subsequent larger scale reduction the two isomers of the *trans*-lactol (**10**) were the only products formed with no sign of the desired *trans*-octahydro-1-benzopyran (**3**; R = H, X = O). The inconsistent nature of this reduction step was overcome by the addition of a quantity of boron trifluoride–diethyl ether to the borane–dimethyl sulphide complex before addition of the lactone. In this way samples of both *cis*- and *trans*-octahydro-1-benzopyran (**2** and **3**; R = H, X = O) were produced by reduction of the lactones (**15**) and (**16**) using the same sample of the borane–dimethyl sulphide complex which had previously led to the formation of the lactol (**10**).

Following completion of our synthesis an alternative route for the synthesis of the isomers of the octahydro-1-benzopyran system was reported as part of a study of the stereoelectronic effect on the decomposition of organic ions in the gas phase.[12] In this latter synthesis a mixture of the lactones (**15**) and (**16**) was reduced to give a mixture of the *cis* and *trans* isomers of the diol (**9**; R = H) which were separated *via* their monobenzoates and then cyclised as their mono-toluene-*p*-sulphonates to give the desired octahydro-1-benzopyran isomers. We had

earlier investigated the use of 88% phosphoric acid for the cyclisation of the diols (**9**; R = H) since it had been reported that 2-(3-hydroxy-1-methylpropyl)cyclohexanol (**9**; R = Me) could be cyclised in the presence of 85% phosphoric acid to give the octahydro-4-methyl-1-benzopyran system.[13] However, we found the major product from the cyclisation of the diols (**9**; R = H) under these conditions to be the isomeric spiro system (**11**) rather than the desired octahydro-1-benzopyran system (**1**; R = H, X = O). We also investigated the cyclisation of the *trans* isomer of the diol (**9**; R = H), prepared by the lithium aluminium hydride reduction of the *trans*-cyclohexanol (**14**), using catalytic hydrogenation conditions with Raney nickel as the catalyst. However, this led to the formation of a mixture of both the *cis* (33%) and *trans* (67%) isomers of the octahydro-1-benzopyran system.

The ^{1}H n.m.r. spectrum of *trans*-octahydro-1-benzopyran is complex even at 400 MHz (Table 1) with the majority of the signals appearing as a complex envelope of overlapping resonances between δ 0.83 and 1.89. Nevertheless, the 2e-H, 2a-H, and 9-H resonances were readily observed at lower field. The loss of a large coupling (11.3 Hz) from the signal at δ 3.96 on irradiation of the signal at δ 3.44 enabled an unambiguous assignment of all three lowfield signals. The *trans*-fused nature of the ring junction was confirmed by the presence of two large ^3J(axial–axial) vicinal couplings (9.2 and 10.4 Hz) to 9-H.

Analysis of the vicinal coupling constants for the C-2 protons (Table 1) enabled the '*R* value'[14] for the C-2–C-3 portion of the ring system to be determined. The calculated '*R* value' of 1.9 corresponds to a dihedral angle along C-2–C-3 of 56° and is in good agreement with the value (1.9) determined previously for tetrahydropyran.[15] It is interesting to note that the 2e-H shows an additional coupling to those arising from the 2a-H, 3e-H, and 3a-H. This coupling (1.7 Hz) is assigned to $^4J_{2e,4e}$ in view of the '*W*' relationship[16] between these protons.

The ^{13}C n.m.r. spectrum of *trans*-octahydro-1-benzopyran (Table 2) compares well with that predicted from a consideration of the shifts in *trans*-decalin together with the substituent effects obtained from a comparison of the shifts in *trans*-tetrahydro-2,3-dimethylpyran[17] and *trans*-1,2-dimethylcyclohexane.[18] In predicting these ^{13}C chemical shifts it was necessary to assume that the γ-*anti* effects on C-5 and C-7, as a result of introducing the oxygen in the decalin ring system, were the same and that the δ-effect on C-6 was very small.

In contrast to *trans*-octahydro-1-benzopyran the corresponding *cis* isomer (**2**; R = H, X = O) has a temperature-dependent ^{13}C n.m.r. spectrum reflecting the conformational mobility of this system. Although the signals were sharp at room temperature there was considerable broadening of all signals apart from the ring-junction carbons C-9 and C-10 at −20 °C. However, by −50 °C the signals had sharpened again indicating that the system had 'frozen out'. Unfortunately, no signals from the minor conformation could be readily observed at low temperatures, indicating that the position of the conformational equilibrium (Type **A** ⇌ Type **E**)* was much more extreme than had been observed in the corresponding nitrogen system *cis*-decahydroquinoline (**2**; R = H, X = NH).[5] Nevertheless, the ^{13}C chemical shifts for the major conformation of *cis*-octahydro-1-benzopyran (**2**; R = H, X = O) (Table 2) compared well with those shifts predicted for the Type **A** conformation.

This interpretation was supported by the 400 MHz ^{1}H n.m.r. spectrum of the *cis*-octahydro-1-benzopyran (**2**; R = H, X = O) which clearly showed the presence of a signal at δ 3.54 which possessed no large couplings ($W_{\frac{1}{2}}$ 11 Hz) (Table 1). Such a signal is highly characteristic of the 9-H ring-junction proton of the *cis* isomer in its Type **A** conformation. As expected, the signals from the two protons on C-2 were also observed at lower field than those from the remaining protons which occurred as a complex envelope of overlapping resonances between δ 1.18—1.87. The signal at δ 3.98, with doublet character, was assigned to the 2e-H, while the other at δ 3.45, having two large couplings, was assigned to the 2a-H.

Unfortunately the smaller couplings were not sufficiently well resolved in the low-temperature ^{1}H n.m.r. spectra of *cis*-octahydro-1-benzopyran to enable their values to be measured accurately. However, since the position for the conformational equilibrium (Type **A** ⇌ Type **E**) observed in the *cis* isomer (**2**; R = H, X = O) at −50 °C had been shown to be extreme, the room-temperature spectra could be assumed to reflect reasonably closely that of the predominant Type **A** conformation. It was therefore possible, from a consideration of the vicinal coupling data obtained from the 2e-H and 2a-H resonances in the room-temperature spectrum of (**2**; R = H, X = O) (Table 1), to show that the '*R* value' for the C-2–C-3 portion of the ring system was 1.9, the same value as that calculated for the *trans* isomer (**3**; R = H, X = O). The presence of a *cis*-fused cyclohexane ring does not, therefore, appear to produce a significant degree of distortion in the pyran portion of the ring system.

Since the *cis*-octahydro-1-benzopyran system (**2**; R = H, X = O) had been synthesised to compare the relative effects of introducing an oxygen and a nitrogen atom into the decalin ring system further efforts were made to establish the conformational ratio (Type **A** ⇌ Type **E**) in this system at low temperatures. Although it could be readily seen from the low-temperature ^{13}C n.m.r. spectrum that the position of the conformational equilibrium (Type **A** ⇌ Type **E**) was more extreme than previously observed for *cis*-decahydroquinoline (**2**; R = H, X = NH),[5] it had been hoped that a more quantitative measure of the difference might have been obtained. Considerable efforts were therefore made to try to observe signals in the ^{13}C n.m.r. spectrum arising from the minor conformation. Spectra were obtained using both 'block averaging' and 'double precision' techniques to maximise the chance of observing any small signals due to the minor conformer. Since the C-2 in the Type **E** conformation of *cis*-octahydro-1-benzopyran (**2**; R = H, X = O) (Table 2) would be expected to resonate at approximately δ 62, this region of the spectrum received particular attention. After several hours of signal accumulation at −70 °C a small but distinct signal was observed at δ 60.1. This signal was significant in that it was only present in the low-temperature spectrum, indicating that it did not arise from a conformationally rigid impurity. Furthermore it could not have arisen from any of the likely *cis* impurities; the *cis*-lactone (**13**),

Table 1. ^{1}H N.m.r. data[a]

	(**2**; R = H, X = O)	(**3**; R = H, X = O)
2e-H	3.98	3.96
2a-H	3.45	3.44
9-H	3.54[b]	2.89[c]
H(others)	1.18—1.87	0.83—1.89
J_{2e2a}	11.3	11.3
J_{2e3a}	4.9	4.6
J_{2e3e}	2.0	1.7
J_{2e4e}	2.0	1.7
J_{2a3a}	12.0	12.3
J_{2a3e}	2.6	2.7

[a] 400 MHz; $CDCl_3$; 25 °C. [b] Half band width 11 Hz. [c] Half band width 27 Hz.

* The Type **A**(**E**) conformation is defined as that where the oxygen is axially (equationally) disposed with respect to the cyclohexane ring.

Table 2. ^{13}C N.m.r. data

Carbon No.	(2; R = H, X = O)[a]			(3; R = H, X = O)[b]		(7)[b]		(8)[b]	
2	68.91	(68.1)[c]	(62.1)[c]	68.28	(67.1)[d]	69.01	(68.9)[e]	68.44	(68.3)[f]
3	20.92	(19.8)	(25.8)	25.78	(26.6)	21.26	(20.9)	26.81	(25.8)
4	29.05	(28.3)	(21.4)	30.71	(30.8)	29.03	(28.8)	30.76	(31.6)
5	34.97	(21.4)	(28.3)	31.90	(32.0)	34.20	(33.9)	40.60	(39.6)
6	25.73	(27.2)	(21.2)	26.82	(27.1)	32.45	(31.4)	32.27	(32.5)
7	20.21	(16.8)	(22.8)	25.07	(24.5)	29.82	(29.1)	33.65	(34.0)
8	31.83	(31.3)	(24.4)	32.56	(33.6)	32.11	(31.8)	32.41	(32.6)
9	75.21	(77.2)	(77.2)	82.02	(83.7)	74.90	(74.9)	82.01	(81.7)
10	34.7	(34.9)	(34.9)	42.14	(41.5)	35.28	(34.7)	41.61	(42.1)
Me						22.72		22.21	

[a] $CDCl_3$–$CFCl_3$ (1:1); −50 °C. [b] $CDCl_3$; 25 °C. [c] Calculated from shifts in *cis*-decalin[5] using oxygen substitution parameters from comparison of shifts in tetrahydropyran and cyclohexane; $\alpha = +40.87$, $\beta = -1.39$, $\gamma = -4.45$ p.p.m. [d] Calculated from shifts in *trans*-decalin[5] using oxygen substitution parameters from comparison of shifts in *trans*-tetrahydro-2,3-dimethylpyran[17] and *trans*-1,2-dimethylcyclohexane.[18] [e] Calculated from shifts in (2; R = H, X = O) with modification for the effect of methyl substitution.[18] [f] Calculated from shifts in (3; R = H, X = O) with modifications for the effect of methyl substitution.[18]

the *cis*-cyclohexanol (**15**) or the *cis* isomer of the diol (**9**; R = H). We have therefore assigned this signal to the C-2 in the Type **E** conformation of *cis*-octahydro-1-benzopyran (**2**; R = H, X = O). Although great caution should be exercised when trying to obtain conformational ratios in such extreme cases our best estimate for the ratio was 99.5:0.5 in favour of the Type **A** conformation at −70 °C, corresponding to a conformational free energy difference of 8.9 kJ mol^{-1}.

This ratio is significantly larger than the situation in *cis*-decahydroquinoline (**2**; R = H, X = NH) where the ratio was found to be 93.5:6.5 in favour of the Type **A** conformation at −74 °C, corresponding to a conformational free energy difference of 4.4 kJ mol^{-1}.[5] However, the increased preference for the Type **A** conformation in *cis*-octahydro-1-benzopyran (**2**; R = H, X = O) with respect to *cis*-decahydroquinoline (**2**; R = H, X = NH) can be readily explained from a consideration of the relative magnitudes of the interactions in the two systems. In the Type **E** conformations the interaction between 2a-H and 8a-H will be greater in *cis*-octahydro-1-benzopyran (**2**; R = H, X = O) than in *cis*-decahydroquinoline (**2**; R = H, X = NH) since the C–O bond length (*ca.* 142 pm) is shorter than that for the C–N bond (*ca.* 148 pm).[19] On the other hand, the reverse situation is found in the Type **A** conformations. Although the shorter C–O bond would bring the heteroatom closer to 5a-H and 7a-H in *cis*-octahydro-1-benzopyran (**2**; R = H, X = O) than in *cis*-decahydroquinoline (**2**; R = H, X = NH) this would be more than offset by the smaller van der Waal's radius of the oxygen (*ca.* 140 pm) in comparison with that of the nitrogen (*ca.* 150 pm).[19]

Further work is in progress on heterocyclic systems containing both oxygen and nitrogen atoms, where the effects of one heteroatom can be offset against the effects of the other, in order to obtain more information about the relative effects of incorporating nitrogen and oxygen atoms into the decalin system.

Experimental

N.m.r. spectra were determined using either a JEOL FX100 or a Bruker WH400 spectrometer.

Octahydro-1-benzopyran (**1**; R = H, X = O).—(i) 3,4-Dihydro-2*H*-1-benzopyran[1] (24.5 g) in cyclohexane (100 cm^3) was hydrogenated in a 1 l steel autoclave initially charged to a pressure of 67 atm using T1 Raney nickel (4 g)[20] as catalyst. The autoclave was heated at 120 °C for 5 h and then allowed to cool. The product was worked up in the usual manner. ^{13}C N.m.r. spectroscopy indicated that, in addition to unchanged starting material (60%), the product contained a mixture of (**2**; R = H, X = O) and (**3**; R = H, X = O) with an isomeric ratio of 91:9. Distillation under reduced pressure using a spinning-band column enabled the octahydro-1-benzopyran (9.2 g, 36%), b.p. 95 °C at 14 mmHg (lit.,[1] b.p. 186—187 °C at 760 mmHg), to be obtained (Found: C, 77.25; H, 11.75. Calc. for $C_9H_{16}O$: C, 77.08; H, 11.5%). The ^1H and ^{13}C n.m.r. spectral data for (**2**; R = H, X = O) and (**3**; R = H, X = O) are given in Tables 1 and 2.

(ii) 3,4,5,6,7,8-Hexahydro-2*H*-1-benzopyran[21] (6 g) in cyclohexane (125 cm^3) was hydrogenated in a 1 l steel autoclave initially charged to a pressure of 6.3 atm for 21 h at 148 °C using T1 Raney nickel (3 g) as the catalyst, and the product worked up in the usual manner. G.l.c. showed the product to be an equal mixture of octahydro-1-benzopyran and starting material. A sample of the octahydro-1-benzopyran was isolated by preparative g.l.c. and shown by ^{13}C n.m.r. spectroscopy to consist of a mixture of (**2**; R = H, X = O) (91%) and (**3**; R = H, X = O) (9%). Further attempts to separate this isomeric mixture by chromatography were unsuccessful.

(iii) *trans*-2-(3-Hydroxypropyl)cyclohexanol (0.9 g) [$\delta_C(CDCl_3)$ 74.08, 62.13, 44.26, 35.47, 30.40, 28.99, 28.11, 25.63, 25.02] prepared by the action of lithium aluminium hydride on *trans*-2-[2-(ethoxycarbonyl)ethyl]cyclohexanol (**14**), was heated at 154 °C for 17 h in an PTFE-lined autoclave (Berghof) with T1 Raney nickel (3.0 g) in an atmosphere of hydrogen (32 atm). The reaction was worked up in the usual manner to give a product (0.8 g) which was shown by ^{13}C n.m.r. spectroscopy to be a mixture of (**2**; R = H, X = O) (33%) and (**3**; R = H, X = O) (67%).

4-(2-*Hydroxyphenyl*)-2-*methylbutan*-2-*ol*. This material was prepared by the action of methylmagnesium iodide on 3,4-dihydro-2*H*-1-benzopyran-2-one.[22] Recrystallisation from chloroform gave the desired product (110 g, 89%) as a white crystalline solid, m.p. 113 °C (lit.,[22] m.p. 111—112 °C) (Found: C, 73.05; H, 8.75. Calc. for $C_{11}H_{16}O_2$: C, 73.3; H, 8.95%); $\delta_C(CDCl_3)$ 153.70(s), 129.79(d), 128.58(s), 127.17(d), 120.14(d), 115.96(d), 71.72(s), 43.07(t), 29.40(q), and 24.71(t).

3,4-*Dihydro*-2,2-*dimethyl*-2H-1-*benzopyran* (**4**; R = Me, X = O). 4-(2-Hydroxyphenyl)-2-methylbutan-2-ol (40 g) was heated under reflux for 15 min with aqueous acetic acid (200 cm^3; 10%) and sulphuric acid (300 cm^3; 50%). The resulting mixture was then extracted with ether. After washing with aqueous sodium hydrogencarbonate solution the combined ether extracts were dried (anhydrous $MgSO_4$). The ether was removed under reduced pressure and the product distilled to

give a colourless liquid (30 g, 83%), b.p. 63 °C at 0.1 mmHg (lit.,[22] b.p. 67.5—68 °C at 2 mmHg); δ_H(60 MHz; $CDCl_3$) 1.3 (s, 6 H), 1.6—1.9 (m, 2 H), 2.55—2.85 (m, 2 H), and 6.55—7.2 (m, 4 H); δ_C($CDCl_3$) 153.63(s), 129.07(d), 126.88(d), 120.38(s), 119.29(d), 116.93(d), 73.59(s), 32.64(t), 26.70(q), and 22.30(t).

Catalytic Hydrogenation of (**4**; R = Me, X = O).—(i) 3,4-Dihydro-2,2-dimethyl-2*H*-1-benzopyran (26 g) in cyclohexane (150 cm^3) was hydrogenated in a 1 l steel autoclave using a 10% palladium-on-charcoal catalyst (1.5 g). The autoclave was charged to a pressure of 78 atm, heated at 115 °C for 1 h, and then allowed to cool slowly. G.l.c. indicated that no starting material remained and that two components had been formed. These were separated by distillation under reduced pressure using a spinning-band column. The major component (69%) (b.p. 89 °C at 20 mmHg) was shown to be a mixture of the *cis* (78%) and *trans* (22%) isomers of *octahydro-2,2-dimethyl-1-benzopyran* (Found: C, 78.5; H, 12.3. $C_{11}H_{20}O$ requires C, 78.51; H, 11.98%). *cis*-Octahydro-2,2-dimethyl-1-benzopyran (**2**; R = Me, X = O), δ_H(100 MHz; $CDCl_3$) 1.19 (s, 3 H), 1.22 (s, 3 H), 1.04—2.02 (m, 13 H), and 3.78 (br s, 1 H); δ_C($CDCl_3$) 71.54(s), 67.36(d), 34.54(d), 32.34(t), 31.95(q), 30.95(t), 26.21(t), 26.04(t), 24.83(t), 22.09(q), and 20.36(t). *trans*-Octahydro-2,2-dimethyl-1-benzopyran (**3**; R = Me, X = O), δ_C($CDCl_3$) 74.60(d), 42.19(d), 37.01(t), 33.12, 31.83, 31.68, 27.42, 25.91, and 25.24 (remaining signals obscured by *cis* isomer).

The second component (31%) (b.p. 119 °C at 16 mmHg) was found to be a mixture of the *cis* (33%) and *trans* (67%) isomers of 2-(3-*methylbutyl*)*cyclohexanol* (**6**) (Found: C, 77.65; H, 13.15. $C_{11}H_{22}O$ requires C, 77.58; H, 13.02%), *cis*-2-(3-methylbutyl)-cyclohexanol, δ_C($CDCl_3$) 74.32(d), 45.24(d), 35.88(d), 35.65(t), 30.16(t), 29.90(t), 28.44(d), 25.62(t), 24.96(t), 22.95(q), and 22.41(q). *trans*-2-(3-methylbutyl)cyclohexanol, δ_C($CDCl_3$) 69.25(d), 41.68(d), 36.49(t), 33.05(t), 29.48, 28.24, 26.68(t), 25.20, 22.71(q), 22.60(q), and 20.68(t).

(ii) 3,4-Dihydro-2,2-dimethyl-2*H*-1-benzopyran (30 g) in cyclohexane (90 cm^3) was hydrogenated in a 1 l steel autoclave using T1 Raney nickel (4 g) as the catalyst. The autoclave was charged to a pressure of 68 atm, heated at 125 °C for 0.5 h, then allowed to cool slowly. After working up the reaction mixture in the usual way the product was examined by ^{13}C n.m.r. spectroscopy. This showed that in addition to the presence of starting material, and the products observed in the previous reduction, there were also signals corresponding to the proposed hydrogenation intermediate, (**5**; R = Me, X = O). Although this component initially accounted for only about 4% of the total product, a highly enriched sample of (**5**; R = Me, X = O) was obtained by fractional distillation of the reaction product (b.p. 93 °C at 18 mmHg). The identity of this component was confirmed to be 3,4,5,6,7,8-hexahydro-2,2-dimethyl-2*H*-1-benzopyran by comparison with an authentic sample, δ_H(60 MHz; $CDCl_3$) 1.25 (s, 6 H), and 1.45—2.1 (m, 12 H); δ_C($CDCl_3$) 144.51, 72.46, 33.53, 28.68, 27.87, 26.46, 23.61, 23.32, and 23.12.

3,4,5,6,7,8-*Hexahydro*-2,2-*dimethyl*-2H-1-*benzopyran* (**5**; R = Me, X = O). This material was made from (**4**; R = Me, X = O) by the method used to prepare 3,4,5,6,7,8-hexahydro-2*H*-1-benzopyran (**5**; R = H, X = O).[21] The crude product was distilled to give the desired compound (7 g, 71%), b.p. 48 °C at 0.08 mmHg (lit.,[23] b.p. 83—84 °C at 12 mmHg) (Found: C, 79.6; H, 10.85. Calc. for $C_{11}H_{18}O$: C, 79.46; H, 10.91%); δ_C($CDCl_3$) 144.36(s), 101.66(s), 72.18(s), 33.46(t), 28.62(t), 27.80(t), 26.41(q), 23.59(t), 23.27(t), and 23.10(t).

3,4-*Dihydro*-6-*methyl*-2H-1-*benzopyran*. 3-(2-Hydroxy-5-methylphenyl)propan-1-ol was prepared by the action of lithium aluminium hydride on 3,4-dihydro-6-methyl-2*H*-1-benzopyran-2-one and then cyclised by the action of phosphorus tribromide [24] to give the 3,4-dihydro-6-methyl-2*H*-1-benzopyran (21 g, 60% overall) as a colourless liquid, b.p. 105 °C at 11 mmHg (lit.,[24] b.p. 111—112 °C at 18 mmHg); δ_H(100 MHz $CDCl_3$) 1.91 (m, 2 H), 2.21 (s, 3 H), 2.68 (t, 2 H), 4.08 (dd, 2 H), and 6.62—6.86 (m, 3 H).

Octahydro-6-*methyl*-1-*benzopyran*. A solution of 3,4-dihydro-6-methyl-2*H*-1-benzopyran (17 g) in cyclohexane (150 cm^3) was hydrogenated at 160 °C in a 1 l steel autoclave (Baskerville) initially charged to a pressure of 80 atm using a 10% palladium-on-charcoal catalyst. The hydrogenation was allowed to continue until the reduction appeared to be complete and the product was then worked-up in the usual way. G.l.c. indicated the product to contain three components; starting material (28%), octahydro-6-methyl-1-benzopyran (49%), and a third component (23%) which was shown by n.m.r. spectroscopy to be a mixture of hydrocarbons. The octahydro-6-methyl-1-benzopyran was isolated by distillation using a spinning-band column and shown by ^{13}C n.m.r. (Table 2) to be a mixture of *cis*-6,10-*cis*-9,10-octahydro-6-methyl-1-benzopyran (**7**) (90%) [δ_H(100 MHz; $CDCl_3$)] 0.92 (br d, Me, 3 H), 1.0—1.9 (complex, 12 H), 3.42 (m, 2e-H, 1 H), 3.49 (br s, 9-H, 1 H), and 3.99 (m, 2a-H, 1 H)], and *cis*-6,10-*trans*-9,10-octahydro-6-methyl-1-benzopyran (**8**) (10%), b.p. 98—100 °C at 14 mmHg (lit.,[24] b.p. 100—101 °C at 25 mmHg) (Found: C, 77.95; H, 11.65. Calc. for $C_{10}H_{18}O$: C, 77.87; H, 11.76%.)

cis- *and* trans-2-[2-(*Ethoxycarbonyl*)*ethyl*]*cyclohexanol* (**13**) *and* (**14**). 2-(Ethoxycarbonylethyl)cyclohexanone[25] (20.4 g) in ethanol (20 g) was hydrogenated in a 150 cm^3 PTFE-lined autoclave (Berghof) at 44 atm using a platinum black catalyst (250 mg) for 17 h at 75 °C and the product worked up in the usual manner. ^{13}C N.m.r. spectroscopy indicated that although some starting material was still present (10%) the major product was a mixture of the two isomers of the desired cyclohexanol in approximately equal quantities.

The reaction mixture (14 g) was separated by medium-pressure column chromatography on Kieselgel 60 (300 g) using ethyl acetate–light petroleum (b.p. 40—60 °C) (20:80) as the eluant. The column was eluted at a rate of 60 cm^3 h^{-1} and the fractions examined by ^1H and ^{13}C n.m.r. spectroscopy. Although the separation of the isomers was incomplete pure samples of both the *cis* isomer (retention time 12—23 h) and *trans* isomer (retention time 21—30 h) were obtained. *cis*-2-[2-(Ethoxycarbonyl)ethyl]cyclohexanol (**13**), δ_H($CDCl_3$) 1.26 (t, 3 H), 1.2—2.5 (m, 14 H), 3.9 (br s, 1 H), and 4.16 (q, 2 H); δ_C($CDCl_3$) 174.38, 68.32, 50.38, 41.15, 32.89, 32.00, 26.73, 26.66, 25.12, 20.42, and 14.23. *trans*-2-[2-(Ethoxycarbonyl)ethyl]cyclohexanol (**14**), δ_H($CDCl_3$) 1.26 (t, 3 H), 0.9—2.8 (m, 14 H), 3.22 (m, 1 H), and 4.17 (q, 2 H); δ_C($CDCl_3$) 173.57, 74.07, 60.35, 44.61, 35.67, 31.53, 30.19, 27.41, 25.53, 24.88, and 14.23.

trans-*Octahydro*-1-*benzopyran*-2-*one* (**16**). *trans*-2-[2-(Ethoxycarbonyl)ethyl]cyclohexanol (7 g) was heated under reflux in benzene (50 cm^3) with toluene-*p*-sulphonic acid (20 mg) in a Dean and Stark apparatus. After 1 h the benzene was removed under reduced pressure and the product distilled under reduced pressure. The desired product (5.1 g, 94%) was obtained as a colourless liquid, b.p. 86 °C at 0.1 mmHg (lit.,[9] b.p. 93—94.5 °C at 0.3 mmHg, unspecified stereochemistry) (Found: C, 69.85; H, 9.3. Calc. for $C_9H_{14}O_2$: C, 70.1; H, 9.15%); δ_H($CDCl_3$) 1.0—2.4 (m, 11 H), 2.4—2.8 (m, 2 H), and 3.7—4.2 (m, 1 H); δ_C($CDCl_3$) 171.19(s), 83.21(d), 38.71(d), 32.24(t), 31.00(t), 29.79(t), 26.43(t), 25.12(t), and 24.05(t).

cis-*Octahydro*-1-*benzopyran*-2-*one* (**15**). *cis*-2-[2-(Ethoxycarbonyl)ethyl]cyclohexanol (9 g) was cyclised in the manner described for the corresponding *trans* isomer except that an additional 1 h of heating under reflux was required to ensure complete cyclisation. The *cis*-octahydro-1-benzopyran-2-one (6.5 g, 94%) was obtained as a colourless liquid, b.p. 88 °C at 0.1 mmHg (lit.,[9] b.p. 93—94.5 °C at 0.3 mmHg, unspecified stereochemistry) (Found: C, 70.0; H, 9.2. Calc. for $C_9H_{14}O_2$: C,

70.1; H, 9.15%); $\delta_H(CDCl_3)$ 1.3—2.3 (m, 11 H), 2.3—2.8 (m, 2 H), and 4.5—4.75 (br s, 1 H); $\delta_C(CDCl_3)$ 172.01(s), 78.03(d), 32.58(d), 30.18(t), 26.82(t), 26.58(t), 24.22(t), 24.22(t), and 20.11(t).

trans-*Octahydro-1-benzopyran* (**3**; R = H, X = O). A freshly opened sample of borane–dimethyl sulphide complex (0.3 cm^3) (see comments in the Discussion section) was added to a stirred solution of *trans*-octahydro-1-benzopyran-2-one (0.4 g) in dry diethyl ether (20 cm^3) under nitrogen. Within a few minutes a white precipitate had formed but this had redissolved after several hours. After 5 h methanol (10 cm^3) and then water (10 cm^3) were cautiously added to the stirred solution. The dimethyl sulphide was removed under reduced pressure on a rotary evaporator and the remaining solution extracted with light petroleum (b.p. 30—40 °C). This extract was dried (anhydrous $MgSO_4$) and the solvent was then removed under reduced pressure (45 °C at 16 mmHg). The product was shown by ^{13}C n.m.r. to be a single component which was identified as *trans*-octahydro-1-benzopyran (0.35 g, 96%) (for n.m.r. data see Tables 1 and 2), M^+ 140. The material was distilled (b.p. 187 °C at 732 mmHg) to give an analytically pure sample (Found: C, 76.85; H, 11.55. Calc. for $C_9H_{16}O$: C, 77.09; H, 11.5%).

cis-*Octahydro-1-benzopyran* (**2**; R = H, X = O). To a solution of boron trifluoride–diethyl ether (1.5 cm^3) in dry diethyl ether (10 cm^3) under nitrogen was added borane–dimethyl sulphide complex (1.8 cm^3). A solution of *cis*-octahydro-1-benzopyran-2-one (1 g) in dry diethyl ether (4 cm^3) was then slowly added. After stirring for 5 h the reaction was worked up using the procedure described for the *trans* isomer. The product (0.5 g, 55%) (M^+ 140) was shown to be *cis*-octahydro-1-benzopyran by comparison with the material produced from the catalytic hydrogenation of 3,4-dihydro-2*H*-1-benzopyran (for n.m.r. data see Tables 1 and 2).

trans-*Octahydro-1-benzopyran-2-ol* (**10**). Using the method previously described for the preparation of *trans*-octahydro-1-benzopyran, *trans*-octahydro-1-benzopyran-2-one (4.5 g) was again reduced with the borane–dimethyl sulphide complex (3 cm^3) (see comments in Discussion section). However, on this occasion no white solid was observed to precipitate during the course of the reaction. The reaction mixture was worked up and extracted with diethyl ether. After drying the extract and removing the solvent a colourless viscous liquid remained (4 g). This product was distilled (b.p. 80 °C at 0.1 mmHg) to give a material which solidified on cooling (m.p. 64—67 °C). This material was shown by n.m.r. to be a mixture of the two isomeric *trans*-octahydro-1-benzopyran-2-ols (lit.,[26] b.p. 98—100 °C at 2 mmHg, m.p. 50—63 °C, unspecified stereochemistry) (Found: C, 69.25; H, 10.5. Calc. for $C_9H_{16}O_2$: C, 69.19; H, 10.33%); $\delta_C(CDCl_3)$ 96.20(d), 91.36(d), 79.63(d), 72.71(d), 41.75, 40.78, 33.29, 32.15, 32.02, 31.64, 31.03, 30.54, 29.42, 25.73, 25.56, 25.07, 24.68, and 24.51.

1-*Oxaspiro*[4,5]*decane* (**11**). 2-(3-Hydroxypropyl)cyclohexanol (10 g, 50:50 mixture of *cis* and *trans* isomers) was added to phosphoric acid (20 g, 88%) in a distillation apparatus. The pressure was reduced to 15 mmHg and the reaction mixture heated and stirred. At about 100 °C a colourless liquid (4.8 g) distilled from the reaction flask. This material was redistilled (b.p. 182 °C at 752 mmHg) to give 1-oxaspiro[4,5]decane (3.0 g) (lit.,[27] b.p. 182 °C at 742 mmHg) (Found: C, 77.05, H, 11.45. Calc. for $C_9H_{16}O$: C, 77.09; H, 11.5%); $\delta_H(CDCl_3)$ 1.0—2.1 (m, 14 H) and 3.65—4.1 (m, 2 H); $\delta_C(CDCl_3)$ 82.08(s), 66.31(t), 37.16(t), 37.16(t), 36.05(t), 25.69(t), 25.69(t), 23.87(t), and 23.87(t).

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