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DIHYDROAROMATIC COMPOUNDS IN THE DIELS–ALDER REACTION—III

IN SITU GENERATION AND DIELS–ALDER REACTION OF CYCLOHEXA-1,3-DIENES

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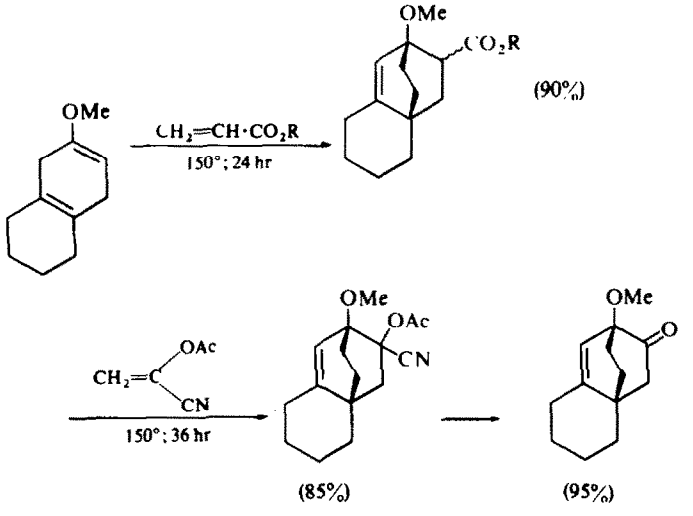
Abstract—Further examples of the synthetic utility of the technique of *in situ* isomerization and Diels–Alder reaction of 2,5-dihydroanisoles are presented. Some of the further chemistry of the products is detailed. The *in situ* generation, and further reactions of 2,3-dihydroanisoles by the pyrolysis of 2-methoxy-1,4-dihydrobenzoic acids is described. This technique constitutes a route to certain cyclohexadienes otherwise difficult of access. The *in situ* isomerization and Diels–Alder reaction of 2,5-dihydroanisoles with acetylene dicarboxylic ester constitutes a convenient and efficient synthesis of substituted phthalic acids.

EARLIER communications[1] have mentioned the technique of *in situ* isomerization of 1,4-dihydroaromatic compounds, and its use in the Diels–Alder synthesis; e.g.



Other examples of the successful use of this technique have recently appeared,[2] and the purpose of this paper is to present further modifications and examples, and to point out some apparent limitations.

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Syntheses based on 2,5-dihydroanisole

The general technique, as described,[1] involved heating the 2,5-dihydroanisole, with an excess of the dienophile, in a sealed tube for several hours. Thus, with methyl acrylate a mixture of the methyl esters of **1a** and **1b** was obtained in good yield, the *endo*-isomer predominating (Table 1). Structures could be assigned on the basis

TABLE 1. DISTRIBUTION OF PRODUCTS IN DIENE SYNTHESIS, AND THEIR EQUILIBRATION

Compound	Percentage in diene synthesis	Percentage on equilibration
1a (Me ester)	30	35
1b (Me ester)	70	65
1c (Me ester)	46	
1d (Me ester)	54	
1e	63	50
1f	37	50
1g	25	
1h	75	
26a (Me ester)	57	60
26b (Me ester)	43	40
28a (Me ester)		50
28b (Me ester)		50
29a (Me ester)	25	36
29b (Me ester)	75	64
30a (Me ester)		56·5
30b (Me ester)		43·5

of the inertness of the angular OMe function to aqueous acid, the known preference[3] of 1-substituted butadienes for Diels–Alder reaction leading to vicinal disubstituted cyclohexenes, and the ready interconversion of the two esters on base-catalysed equilibration. The *endo*-configuration was assigned to the more abundant isomer at equilibrium. This assignment was supported by the NMR signal associated with the ester OMe group which occurred at higher field than that of the *exo*-isomer (Table 2), the ester function being within the shielding cone of the double bond.[1a]

GLC analysis of the Diels–Alder reaction product revealed the presence of four minor components (total 10%) which were separated by preparative GLC. Their NMR spectra were not readily interpretable, but two of them contained no bridgehead OMe function. Oligomers of acrylic ester were probably present, and the possibility of an 'ene'-reaction[4] between 2,5-dihydroanisole and acrylic ester, competitive with the isomerization-Diels–Alder sequence and leading to the esters **4** or **5** must also be considered.* This type of reaction did not occur to greater than 1·5% of the total. A third minor component (~3%) had an NMR spectrum in accord with it being a

* For an example of this type of reaction in a similar context, see ref. 25.

TABLE 2. PRINCIPAL NMR RESONANCES (ppm; TMS INTERNAL STANDARD)

Compound (solvent; if other than CCl_4)	Olefinic protons	—OMe	—CO_2Me	—Me	Other
1a-methyl ester	6·25(m)	3·36(s)	3·69(s)		
1b-methyl ester	6·12(m)	3·30(s)	3·56(s)		
1c-methyl ester	6·1(m)	3·13(s)	3·50(s)	0·99(s)	
1d-methyl ester	6·1(m)	3·16(s)	3·39(s)	1·20(s)	
1e	6·28(m)	3·40(s)			
1f	6·34(m)	3·40(s)			
1g	6·27(m)	3·35(s)			2·16(s)-$COCH_3$
1h	6·16(m)	3·34(s)			2·05(s)-$COCH_3$
1k	6·20(m)	3·23(s)			2·45(m)-allylic
2a-methyl ester		3·10(s)	3·61(s)		
2c		3·15(s)			2·13(s)-$COCH_3$
6	6·20(m)	3·33(s)		0·97(d)	
7	6·30(m)	3·42(s)		1·14(d)	
8	6·30(m)	3·32(s)		1·12(d)	
9 and **10**		3·10(s); 3·18(s)		1·03(d); 1·09(d)	
11a ($CDCl_3$)	4·87	3·49(s); 3·51(s)			
11b		3·42(s); 3·50(s)		1·53(s)	
12a (pyr.)		3·32(s)			
12b (pyr.)		2·95		0·80(d)	
13a	6·0–6·6(AB-X)	3·37(s)			
13b	6·02–6·68(AB-X)	3·33(s)		1·0(d)	
13c	6·02–6·68(AB-X)	3·31(s)		0·98(d)	
1,3-Dimethoxy-2-methyl-2,5-dihydrobenzene	4·50(t)	3·50(s)		1·15(d)	
21 ($CDCl_3$)	4·77(d); 5·45(m)	3·65(s)			10·84(s)-CO_2H
23a					
23b					1·75(m)-CH_2— 2·70(m)-benzylic—CH_3— 4·62(s)-$COCH_2$—Cl 6·70(s)-aromatic 7·35(s)-aromatic
24a		3·92(s)			6·6(s) 7·65(s)-aromatic
24b ($CDCl_3$)		4·10(s)			7·80(s)-aromatic
24c ($CDCl_3$)					6·84(s)-aromatic 7·74(s)-aromatic 9·80(s)-CO_2H
26a and **26b** ($CDCl_3$)	5·87–6·47(AB)	3·34(s); 3·38(s)	3·63(s); 3·68(s)		

m = multiplet; s = singlet; d = doublet; AB-X = AB part of ABX spectrum; t = triplet; AB = spectrum.

mixture of the structures (3). While not rigorously proven, it is possible to say that the minimum ratio of 2- to 3-carboxylates produced in this reaction is 25:1.[5]*

Hydrogenation of the esters **1a** and **1b** gave the saturated ester **2a**.

A similar reaction sequence with methyl methacrylate led to the esters of **1c** and **1d** with little preference for the *endo* isomer. The NMR signals used in the assignment of structure are listed in Table 2. Hydrogenation of either ester gave the saturated ester **2b**.

LAH reduction of the esters of **1** and **2** gave the corresponding primary alcohols. The solvolytic behaviour of the tosylates has been studied and will be reported elsewhere. A brief report of part of this work has appeared.[6]

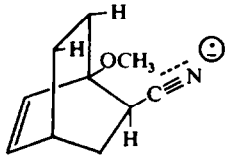
With acrylonitrile, a high yield of the nitriles **1e** and **1f** was obtained; the *exo*-isomer predominating. Configurations were confirmed by hydrolysis to the known acids. They were separated by preparative GLC and individually reduced to the amines, either with LAH or lithium in liquid ammonía. In the latter case a minor product was also obtained,† the spectroscopic data for which suggested the structure **1k**. Reductive cleavage of the C—CN bond has been reported previously.[7] The deamination of these primary amines has been studied, and will be reported elsewhere.

With methyl vinyl ketone, a good yield of the ketones **1g** and **1h**, separable by preparative GLC was obtained.[2a] Reduction with LAH led, in the case of the *endo*-isomer **1h** to a single alcohol, as judged by the single peak on GLC analysis over various stationary phases, and the single OMe signal of the NMR spectrum. However, tosylate formation yielded a crystalline derivative, and a partially crystalline residue, which behaved somewhat differently on solvolysis. This suggests, but does not require, the presence of ~10% of the epimeric alcohol, presumably having very similar physical properties. This conclusion is rendered less clear by the known presence of a small amount (~3%) of one of the *exo*-alcohols as an impurity.

Reduction of the *exo*-isomer (**1g**) gave two alcohols, in the ratio of 55:45 as indicated by GLC analysis and integration of the OMe signals of the NMR spectra. These alcohols were readily separated by preparative GLC. The more abundant isomer was assigned the *R*-configuration‡ (7) at the side-chain C atom on the following grounds:

* It is worth noting that no trace of adducts derived from 3,4-dihydroanisole were detected in this reaction.

† The *exo*-nitrile (**1e**) was more susceptible to this type of cleavage (7·2% yield) than was the *endo*-isomer (0·5% yield). It is tempting to attribute this difference to greater relief of strain on cleavage of the *exo*-isomer probably via the solvated anion-radical (i)



i

‡ All the compounds discussed were racemic. The symbols *R*- and *S*- refer to those enantiomers illustrated, having the *R*-configuration at the bridgehead carbon bearing the methoxyl group.

(i) The more ready elution on GLC was in accord with intramolecular H bonding between the OH and OMe groups. Figure 1 shows the non-bonded interactions which might be expected to prevent H-bonding in the isomer of *S*-configuration (**8**).

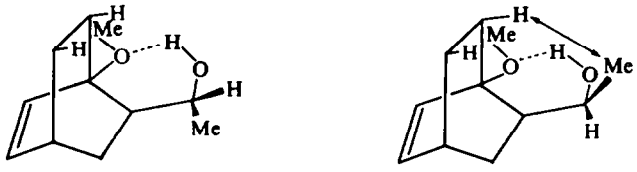


FIG. 1

(ii) The OMe signal in the NMR spectrum (Table 2) was at lower field than that of the epimeric alcohol. This observation was taken to support the idea of intramolecular H-bonding.[8]

(iii) The solution IR spectrum revealed the presence of intramolecular H-bonding, that of the epimeric alcohol showing only intermolecular bonding, (Fig. 2).

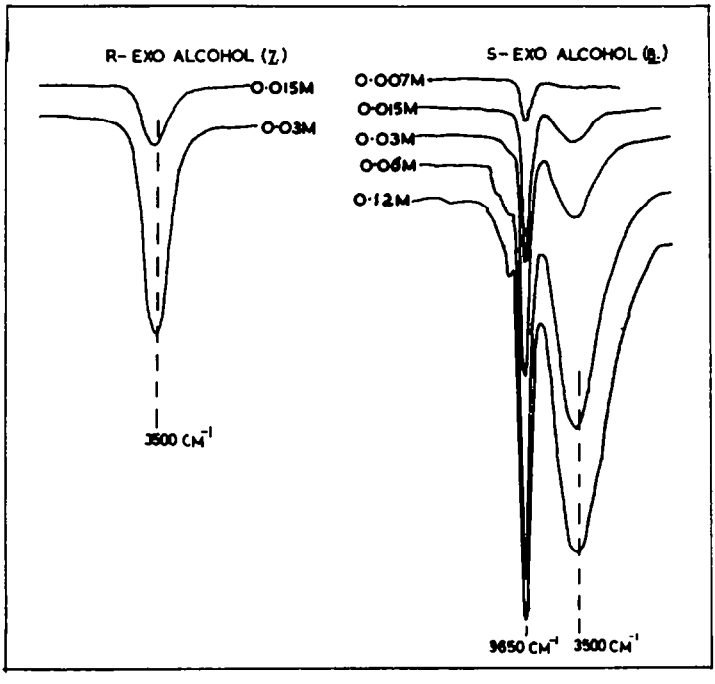
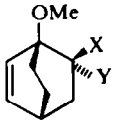


FIG. 2

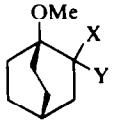
Hydrogenation of the two ketones **1g** and **1h** gave the saturated ketone **2c**, LAH reduction of which furnished the two alcohols **9** and **10** in the ratio of 2:3, to which structures were assigned on the basis of arguments similar to those just outlined.

The acid-catalysed dehydrations of the alcohols **7**–**10** and solvolyses of their tosylates are entirely in accord with the configurations assigned. Further, on the basis of the solvolysis results, which will be reported elsewhere, it was possible to assign the *R*-configuration to the side-chain carbon atom of the *endo*-alcohol **6**.



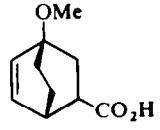
1

a: X = CO_2H; Y = H
b: X = H; Y = CO_2H
c: X = CO_2H; Y = Me
d: X = Me; Y = CO_2H
e: X = CN; Y = H
f: X = H; Y = CN



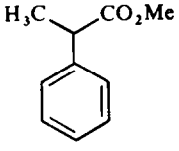
2

g: X = COMe; Y = H
h: X = H; Y = COMe
i: X = COMe; Y = Me
j: X = Me; Y = COMe
k: X = Y = H



3

a: X = CO_2H; Y = H
b: X = CO_2H; Y = Me
c: X = COMe; Y = H



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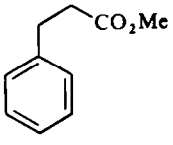

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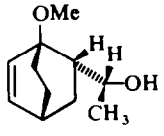

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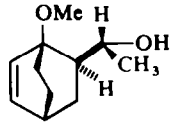

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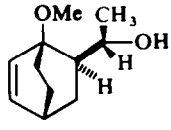
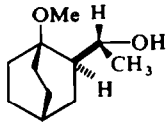
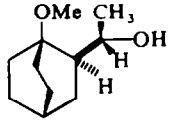


8



9



10

An attempt to synthesise the related ketones **1i** and **1j** by use of isopropenyl methyl ketone, gave rise to a complex mixture of products. Preparative GLC, and NMR analysis revealed that the required ketones were present in only very minor amounts. Pre-equilibration of the dihydroanisole, followed by reaction with isopropenyl methyl ketone at lower temperatures gave slightly improved yields of the required ketones, but the method remained impractical.

Syntheses based on 2,5-dihydroresorcinol dimethyl ether

In connection with our investigations of the solvolytic reactions of OMe substituted bicyclo[2.2.2]-octenyl tosylates, it became necessary to develop a convenient synthesis of the ketones **13a**–**c**. A reasonable starting point seemed to be the adduct of 4,5-dihydroresorcinol dimethyl ether with maleic anhydride, **11a**.

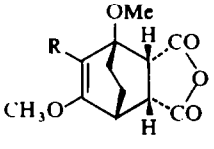
Attempted *in situ* isomerization and Diels–Alder reaction of 2,5-dihydroanisole with maleic anhydride as dienophile proved to be unpromising in our hands, yielding only polymeric material. On the basis of this experience, our first attempts at synthesis of the adduct **11a** involved preequilibration of 2,5-dihydroresorcinol dimethyl

ether and subsequent reaction with maleic anhydride. This gave, in modest yield, a product, the NMR of which (Table 2) was entirely in accord with structure **11a**.

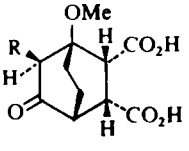
Subsequently, it was discovered that *in situ* isomerization and reaction with maleic anhydride of the 2,5-dihydroresorcinol dimethyl ether could be achieved by simply refluxing the reagents together in benzene solution for 24 hr. Surprisingly, the addition of glass-wool to the reaction vessel brought about very rapid *in situ* equilibration and reaction at room temperature. In the case of 2-methyl-2,5-dihydroresorcinol dimethyl ether the reaction was less facile, extended refluxing in presence of glass-wool being required, when a good yield of the adduct **11b** was obtained.

This difference in reactivity was taken to reflect the lowering in acidity produced by the Me substituent (probably ~2 pK units[9]), the glass-wool functioning as a basic catalyst. However, subsequent work on the *in situ* isomerization and Diels–Alder reaction of 2,5-dihydroresorcinol dimethyl ether with methyl acrylate has revealed that no reaction occurs below 150° in a sealed tube, under which conditions fair yields are obtained.[10] It seems therefore that the low temperature *in situ* isomerization is also a function of the reactivity of the dienophile. Thus, in the examples quoted, the acidity of the methylene protons might be enhanced by complex formation between the enol ether and the maleic anhydride. More recently we have learnt (personal communication from Professor A. J. Birch), that 2,5-dihydroanisole reacts at room temperature with maleic anhydride to give the adduct derived from 2,3-dihydroanisole. This would appear to be in accord with the idea of base (glass-surface) catalysed equilibration of a preformed complex in the case of reaction with maleic anhydride, and similarly catalysed equilibration of the uncomplexed diene in the case of reaction with methyl acrylate and other less reactive dienophiles.

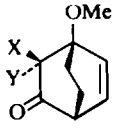
Hydrolysis of **11a** to the keto-diacid **12a** was best achieved by heating in aqueous glyme followed by removal of the solvents. By deferring purification to this stage, very high yields based on resorcinol dimethyl ether could be easily obtained. Oxidative decarboxylation using lead tetraacetate in pyridine gave the ketone **13a** in fair yield.[11]



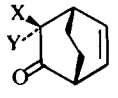
11
a: R = H
b: R = Me



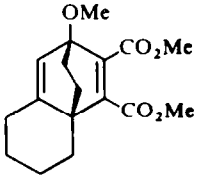
12
a: R = H
b: R = Me



13
a: X = Y = H
b: X = Me; Y = H
c: X = H; Y = Me



14
a: X = Y = H
b: X = Me; Y = H
c: X = H; Y = Me
d: X = Y = Me



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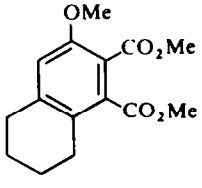

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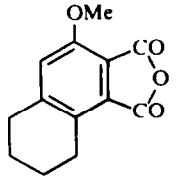

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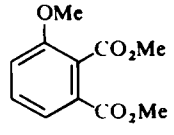


18

Hydrolysis of **11b** gave a keto-diacid, the Me doublet in the NMR spectrum of which indicated that it was a single epimer. The structure **12b**, containing an *exo*-Me group was assigned on the basis of the following evidence. Oxidative decarboxylation led to a single ketone, which on base-catalysed equilibration furnished a mixture of ketones, inseparable on GLC, the NMR spectrum of which indicated the presence of a new compound, present in excess (~65%) the Me doublet of which was shifted to higher field. These results are in accord with the original ketone **13b** and hence the keto-diacid **12b** having an *exo*-Me group, equilibration leading to the more stable *endo*-methyl isomer **13c** in which shielding of the Me group by the double bond is to be expected. They are also in accord with the NMR spectra and equilibration behaviour of the ketones **14b–14d** obtained by alkylation of bicyclo[2.2.2]oct-5-en-2-one.[25]

The exclusive production of the *exo*-Me epimer **12b** on hydrolysis of the adduct **11b** deserves comment. Presumably, in aqueous glyme, this proceeds via the uncatalysed hydrolysis of the anhydride grouping, followed by intramolecular protonation of the enol-ether, either directly by the carboxyl group or through a water molecule as shown in Fig. 3. Intermolecular hydrolysis, by carboxyl or hydroxonium ion would be expected to lead to a mixture, probably with the *endo*-Me epimer predominating, because of the hindrance to approach to the *endo*-face of the molecule; cf. hydrogenation of the acid **29b**.[1a]

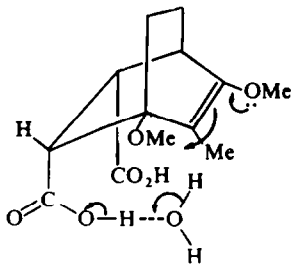


FIG. 3

Syntheses using acetylene dicarboxylic ester

An attempted synthesis of the tricyclic diester **15** via *in situ* isomerization and Diels–Alder reaction with acetylene dicarboxylic ester, of 6-methoxy-1,2,3,4,5,8-hexahydronaphthalene gave directly, and in high yield, the methoxytetralin dicarboxylic ester **16**, presumably by thermal extrusion of ethylene from the initial adduct **15**. Pre-equilibration of the methoxyhexalin, followed by Diels–Alder reaction with acetylene dicarboxylic ester at room temperature gave the tricyclic adduct **15**. This compound readily lost ethylene at 140°.

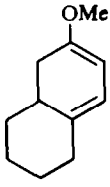
This sequence of reactions would seem to be a simple and valuable technique for introducing two carboxyl functions into a substituted anisole. Thus anisole itself, by reduction, *in situ* isomerization and reaction with acetylene dicarboxylic ester, may be converted into 3-methoxyphthalic ester **18** in an overall yield of ~85%.[12]

Syntheses based on 1,4-dihydrobenzoic acids

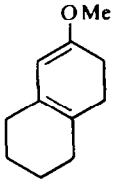
In connection with other synthetic work, it became necessary to have access to

adducts of the diene **19**, isomeric with **20** obtained on Birch reduction and *in situ* isomerization of 6-methoxytetralin.[1] Our first essays in this area involved the attempted hydrolysis and decarboxylation of the 1,4-dihydroacid **21** to the ketone **25**. It was hoped that enol-etherification would then furnish the required diene. In the event, the hydrolysis step gave only very poor yields of ketonic materials, either with the acid **21** or the simpler 1,4-dihydro-2-methoxybenzoic acid **22**, a result in keeping with previous experiments.[13*]

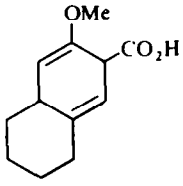
The pyrolytic decarboxylation of acids such as **21** and **22** seemed a possible route to dienes of the type required since (a) the decarboxylation of βγ-unsaturated acids



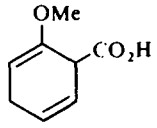
19



20



21



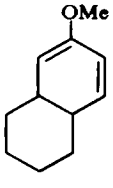
22

occurs with migration of the double bond, (b) of the two isomeric dienes obtainable in this way, that required is the more stable, having a terminal OMe group and (c) the decarboxylation involves, in acyclic systems at least, proton transfer from the carboxyl group to the double-bond in the rate-determining step,[14] migration of the more nucleophilic (OMe-substituted) double bond would be expected.

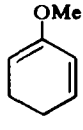
Pyrolysis of the acid **22**, under a variety of conditions gave very poor yields of volatile materials, in which 2,3-dihydroanisole and the cyclohexenones could be detected spectroscopically. Pyrolysis in a sealed tube, in presence of an excess of ethyl acrylate gave a modest yield (40%) of the ethyl esters corresponding to **1a** and **1b**. 1,4-Dihydro-benzoic acid gave a similarly modest yield of the epimeric bicyclo[2.2.2]oct-5-ene-2-carboxylates, while 1,4-dihydro-*m*-toluic acid did not yield recognisable products.

The application of this reaction sequence to the acid **21** required the development of a convenient preparation of the methoxytetralin carboxylic acid **24a**. The published route via Kolbé carboxylation of 6-hydroxytetralin[13] was not successful in our hands. Friedel–Crafts acetylation of 6-methoxytetralin gave the ketone **23a** in good yield,

* Recent work on the *in situ* enol-acetylation of cyclohex-2-enones, and Diels–Alder reaction of the products[15] suggests that our proposed route might have produced dienes (i) and (ii) in addition to the expected 1-methoxycyclohexa-1,3-dienes.

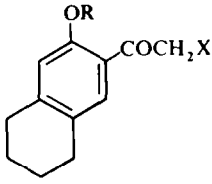


i



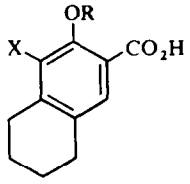
ii

but conversion to the acid via haloform reaction proceeded in poor yield, and led to nuclear halogenated products; e.g. **24b**.



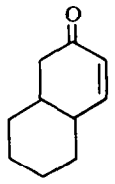
23

a: X = H; R = Me
b: X = Cl; R = H
c: X = Cl; R = Me

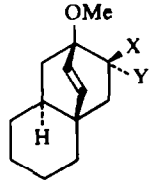


24

a: X = H; R = Me
b: X = Cl; R = Me
c: X = R = H

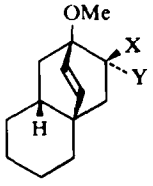


25



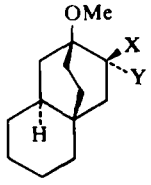
26

a: X = CO_2H; X = H
b: X = H; Y = CO_2H



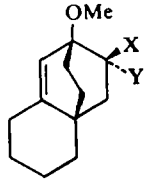
27

a: X = CO_2H; Y = H
b: X = H; Y = CO_2H



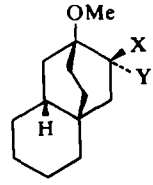
28

a: X = CO_2H; Y = H
b: X = H; Y = CO_2H



29

a: X = CO_2H; Y = H
b: X = H; Y = CO_2H

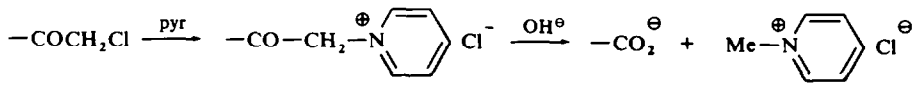


30

a: X = CO_2H; Y = H
b: X = H; Y = CO_2H

The use of chloroacetyl chloride in the Friedel–Crafts reaction gave not the expected ketone **23c**, but the demethylated product **23b** in poor yield. Good yields of this compound were obtained by using 6-hydroxytetralin as a substrate.

The reaction sequence[16]:—



proceeded in fair yield to the hydroxy acid **24c** methylation of which with dimethyl sulphate in strongly alkaline solution* furnished the methoxy acid **24a** together with the corresponding ester as a minor product. Lithium in ammonia reduction of the acid gave the required 1,4-dihydrobenzoic acid **21**. The NMR spectrum was entirely in accord with this structure.

Pyrolysis in the presence of methyl or ethyl acrylate led to the production of a mixture of esters in 60% yield. GLC analysis revealed the presence of two major components (esters of **26a** and **b**) in the ratio of 3:1. Minor components, amounting to less than 10% of the total, may have been the esters of the epimeric acids **27a** and **b**, although their structures were not elucidated.

* The conditions used were those developed by us for the one-step preparation of O-methylpodocarpic acid from podocarpic acid.[17] More recently, details of a very similar process have appeared.[18]

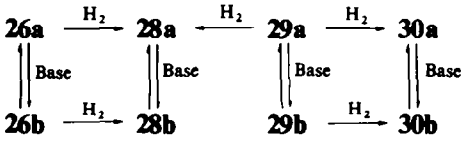
The structures **26a** and **26b** for the major components of the hydrolysed ester mixture were established on the basis of the following evidence:—

(a) The two Me esters were interconverted on treatment with potassium *t*-butoxide in t-butanol. The more abundant ester (see Table 1) was assumed to have the carbomethoxyl function *endo*- with respect to the double bond; a conclusion supported by the NMR spectrum.

(b) The vicinal relationship of the OMe, shown to be at the bridgehead by its inertness to acid, and the carboxyl function was assumed on the basis of the known specificity of the diene **20** in the Diels–Alder reaction with ethyl acrylate.[1a] This assumption is borne out by the correlation with compounds of established structure mentioned below.

(c) The NMR spectrum of the mixed Me esters showed signals at δ 3·34 and 3·38 ppm (—OMe; 3:1), at δ 3·63 and 3·68 ppm (CO_2Me; 3:1) and at $\sim\delta$ 6·1 ppm as a complex multiplet integrating for two protons. This region could be interpreted as two AB spectra, partially superimposed, with $J_{AB} = 9$, and centred at δ 6·1 and δ 6·25 ppm (3:1). This shift, due to the shielding of the vinyl protons by the ester function in **26a** is comparable to that observed in the vinyl region of the NMR spectra of the esters of **29**.[1a]

(d) Hydrogenation of the Me ester of the more abundant acid **26a** gave a product **28a** methyl ester, having the same retention time on GLC analysis as one of the products of hydrogenation of the known ester of **29a**. Further the Me ester of structure **28a** obtained by the hydrogenation route, on equilibration under basic condition, gave an ester **28b** having the same retention time as the product of hydrogenation of the methyl ester of the minor product **26b**. The relationships referred to are illustrated in the following reaction scheme.

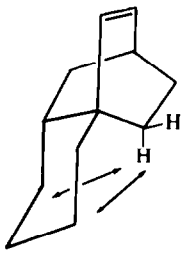


Methyl esters

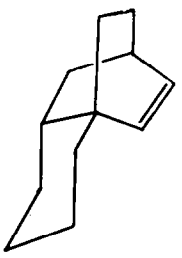
The various equilibration results are listed in Table 1.

The production of predominantly the esters of the acids **26** rather than of the epimeric acids **27** in this Diels–Alder reaction, deserves comment. The equilibration data gathered together in Table 1 reveals that in the bicyclo[2.2.2]oct-5-ene-2-carboxylic esters, the *endo*-isomer is the stabler by a small factor ($\Delta G \sim$ 0·3–0·6 Kcals/mole). It is reasonable to expect on this basis, that the ring system **31** would be less stable then the epimeric system **32** by a considerably larger factor, since effectively two alkyl groups are in the *exo*-environment and since in the cyclohexyl series, alkyl groups appear to be more sterically demanding than carbomethoxyl groups.[19] Since it is believed that the transition state geometries for some Diels–Alder reactions are well along the reaction coordinate towards product geometries,[20] then at least part of this free energy difference should be reflected in the activation free energies of the reactions leading to esters of the type **26** on the one hand **27** on the other.

Such considerations seem adequate to account for the observed specificity. A recent publication[24] on the Diels–Alder reactions of 5-methylcyclopenta-1,3-diene, reveals a very similar stereospecificity.



31



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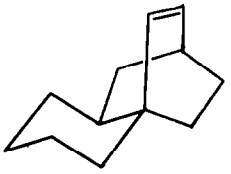

32

EXPERIMENTAL

GLC analyses were performed on a Pye 104 Model 34 flame ionization gas chromatograph over polyethylene glycol adipate as a stationary phase except where otherwise indicated. Other stationary phases used were polyethylene glycol succinate (PEGS), silicone gum rubber (SE 30) and Apiezon L (APL). Preparative GLC was performed on an F & M Model 775 "Prepmaster", using 0·75 in. diameter columns, 8 ft and 16 ft in length and a PEGA stationary phase. Small scale preparative GLC was performed on a Pye 104 Model 34 GLC using a 9 ft × 0·25 in. stainless steel column and a 10% PEGA stationary phase, and a Pye preparative modification unit.

1-*Methoxybicyclo*[2.2.2]*oct-5-en-2-yl carboxylic acids* (**1a** *and* **1b**)

Crude 2,5-dihydroanisole obtained by Li in ammonia reduction of anisole[21] (23·5 g) was heated in a sealed tube with methyl acrylate (40 g) and hydroquinone (0·5 g) under N_2, at 150° for 30 hr. Unchanged acrylate was removed and the residue taken up in ether, washed with cold 2% NaOH aq, dried and evaporated. Distillation gave a colourless liquid (28 g; 60%); b.p. 80°/0·15 mm; ν_{max} 1725 cm^{-1}. GLC analysis at 140° revealed the presence of the Me esters of **1a** (25·8%) and **1b** (61·8%) and minor components (3·6, 1·4, 3·9 and 3·6% respectively). The esters were readily separated by preparative GLC. The NMR spectra of the pure esters are listed in Table 2. The minor component showed *inter alia* the following main features:*

(A) Two or more partially overlapping quartets centred at ~δ 4·1 ppm ($CO_2C\underline{H}_2Me$); several signals in the region δ 1·1–1·5 ppm ($CO_2CH_2C\underline{H}_3$); a complex signal centered at δ 6·2 ppm (olefinic protons) and a broad singlet at δ 7·2 ppm (aromatic protons).

(B) A complex multiplet at δ 6·1 ppm (olefinic protons), a quartet at δ 6·0 ppm (CO_2CH_2Me) and complex signals at δ 1·0–1·3 ppm.

(C) A singlet at δ 3·3 ppm (OMe); two quartets at δ 4·1 and δ 4·15 ppm; two triplets at δ 1·15 and δ 1·25 ppm and a complex multiplet at δ 4·2 ppm. The fourth minor component was not isolated.

The two adducts were also readily separated by hydrolysis to the acids and column chromatography on silica gel using ether/light petroleum (1 : 4) as the eluent. The *exo*-isomer (**1a**) was eluted first.

Exo-*isomer* **1a** had m.p. 83·5–85°. (Found: C, 65·99; H, 7·45. $C_{10}H_{14}O_3$ requires: C, 65·90; H, 7·70%).

Endo-*isomer* **1b** had m.pt. 108–109°. (Found: C, 66·16; H, 7·70. $C_{10}H_{14}O_3$ requires: C, 65·90; H, 7·70%).

Exo- *and* endo-1-*methoxybicyclo*[2.2.2]*oct-5-en-2-yl methanols*

The *exo*-acid **1a**, (2·42 g) was reduced with LAH (3 g) in ether. The product was obtained as a colourless oil (1·79 g; 80%). The *tosylate* had m.p. 35–36°. (Found: C, 63·69; H, 6·63. $C_{17}H_{22}O_4S$ requires C, 63·30; H, 6·84%).

The *endo*-acid (3 g) was similarly reduced to the methanol (1·5 g, 54%). The *tosylate* had m.p. 54–55°. (Found: C, 63·38; H, 6·91; S, 9·90. $C_{17}H_{22}O_4S$ requires: C, 63·30; H, 6·84; S, 9·94%).

* The minor components were separated from a reaction mixture obtained using ethyl acrylate. No change in the pattern of products was observed in changing from ethyl to methyl acrylate.

1-*Methoxybicyclo*[2.2.2]*octan-2-yl carboxylic acid* (**2a**)

Hydrogenation of (**1a** *or* **b**) in MeOH under atmospheric press, over a PtO_2 catalyst gave a single oily product; ν_{max} 1725 cm^{-1}. Hydrolysis gave the acid, m.p. 115–116°. (Found: C, 65·88; H, 8·87. $C_{10}H_{16}O_3$ requires: C, 65·19; H, 8·75%).

1-*Methoxybicyclo*[2.2.2]*octan-2-yl methanol*

The acid **2a** (2·47 g) was reduced with LAH (0·62 g) in ether to the alcohol 1·86 g (82%). The *tosylate* had m.p. 68–69°. (Found: C, 62·92; H, 7·51; S, 9·99. $C_{17}H_{24}O_4S$ requires: C, 62·96; H, 7·41; S, 9·88%).

1-*Methoxy-2-methylbicyclo*[2.2.2]*oct-5-en-2-yl carboxylic acids* (**1c** *and* **1d**)

2,5-Dihydroanisole (40 g), methyl methacrylate (73 g) and hydroquinone (1·8 g) when reacted together as detailed above, yield a mixture of esters (36 g; 65%); b.p. 80–100°/0·1 mm; ν_{max} 1725. The *exo*-carboxylate was eluted first on GLC, the *endo*-isomer being present in excess (1·7:1). Hydrolysis and chromatography on silica gel gave the pure acids after crystallization from light petroleum. exo-*acid* **1c** had m.p. 139°. (Found: C, 67·23; H, 8·24. $C_{11}H_{16}O_3$ requires: C, 67·40; H, 8·17%). The endo-*acid* **1d** has m.p. 136°. (Found: C, 67·13; H, 8·26. $C_{11}H_{16}O_3$ requires: C, 67·40; H, 8·17%).

1-*Methoxy-2-methyl bicyclo*[2.2.2]*oct-5-ene-2-yl methanols*

The *exo*-acid **1c** (3·8 g) was reduced with LAH (1·2 g) in ether, to the alcohol (3·4 g; 90%). The tosylate had m.p. 80°. (Found: C, 64·53; H, 7·16; S, 9·08. $C_{18}H_{24}O_4S$ requires: C, 64·3; H, 7·15; S, 9·52%).

The *endo*-acid **1d** (4·0 g) was similarly reduced to the alcohol (3·2 g; 80%). The *tosylate* had m.p. 83°. (Found: C, 63·94; H, 7·19. $C_{18}H_{24}O_4S$ requires: C, 64·3; H, 7·15%).

1-*Methoxy-2-methylbicyclo*[2.2.2]*octan-2-yl carboxylic acid* (**2b**)

The mixed acids **1c** and **1d** (3g) were hydrogenated in MeOH, under atmo press, over a 10% PdC catalyst. The product, after crystallization from light petroleum (2·76 g; 91%) had m.p. 146°. (Found: C, 66·33; H, 9·48. $C_{11}H_{18}O_3$ requires: C, 66·60; H, 9·10%).

1-*Methoxy-2-methylbicyclo*[2.2.2]*octan-2-yl methanol*

The acid **2b** (2·76 g) was reduced with LAH to the alcohol (2·4 g; 95%). The *tosylate* had m.p. 93°. (Found: C, 64·36; H, 8·17; S, 9·60. $C_{18}H_{26}O_4S$ requires: C, 64·0; H, 7·70; S, 9·47%).

1-*Methoxy-2-cyano-bicyclo*[2.2.2]*oct-5-enes* (**1e** *and* **1f**)

2,5-Dihydroanisole (15 g), acrylonitrile (15 g) and hydroquinone (0·1 g) were heated together in a sealed tube, under N_2 to 120° for 60 hr. The volatile materials were removed and the residue extracted thoroughly with ether, the extract being washed with 2% NaOHaq, dried and evaporated. Distillation gave 15·2 g of a colourless oil; b.p. 50–110°/0·15 ml, GLC analysis of which showed it to be a 96% pure mixture of **1e** and **1f**, the *exo*-isomer **1e** predominating (Table 1). The isomers were separated by preparative GLC.

Equilibration using t-butoxide in t-butanol afforded a 1:1 mixture of epimers.

Hydrolysis using 10% aqueous KOH afforded the acids **1e** and **1f**.

Reduction of 1-*methoxy-2-cyanobicyclo*[2.2.2]*oct-5-enes*

(a) The mixed nitriles (1 g) in dry ether (20 ml) were added to a suspension of LAH (1·4 g) in dry ether and the mixture refluxed for 4 hr. The excess LAH was destroyed by addition of water and the soln filtered. The ether extract was washed, dried and evaporated to yield a mixture of the corresponding primary amines (0·09 g; ~8%). The yield by this method could not be improved.

(b) Compound **1f** (2 g) in MeOH (10 ml) was added to liquid ammonia (300 ml) and Na (3 g) added in small pieces over 1 hr. Evaporation of the ammonia followed by extraction with ether, washing with water, drying and evaporating gave the endo-1-*methoxybicyclo*[2.2.2]*oct-5-en-2yl methylamine*, (1·7 g) as a viscous oil; *tosyl derivative*, m.p. 73–75°. (Found: C, 63·85; H, 7·24; S, 10·08. $C_{17}H_{23}O_2NS$ requires: C, 63·54; H, 7·21; S, 9·96%).

After deamination, 1-*methoxybicyclo*[2.2.2]*oct-2-ene* (**1k**) was identified as an impurity (0·5% of amine).

The *exo*-nitrile was similarly reduced to give the exo-1-*methoxybicyclo*[2.2.2]*oct-5-en-2-yl methyl amine* as a viscous oil. **1k** was identified as an impurity after deamination (7·2% of amine).

1-Methoxy-2-acetylbicyclo[2.2.2]*oct-5-enes* (**1g** *and* **1h**)[2a]

2,5-Dihydroanisole (43 g) and freshly distilled methyl ketone (65 g), together with hydroquinone (1·6 g) were heated in a sealed tube, under N_2, for 39 hr at 160°. Removal of excess dienophile followed by distillation gave a mixture containing about 50% of the required ketones; b.p. 50–90°/0·01 mm, ν_{max} = 1715 cm^{-1}. Preparative GLC gave the adducts in better than 95% purity, the impurity in each case being the epimeric ketone.

The *exo*-ketone **1g** was first eluted and had ν_{max} 1705 cm^{-1}. The NMR spectra are analysed in Table 2. The *endo*-ketone **2h** had ν_{max} 1705 cm^{-1}.

1-Methoxy-2-acetylbicyclo[2.2.2]*octane* (**2c**)

Hydrogenation of the mixed ketones **1g** and **1h** over a 10% PdC resulted in a complex mixture of products which was not investigated further. Hydrogenation of the *endo*- **1h** (0·5 g) in MeOH gave a product containing two components in the ratio of 1:1·05 as shown by GLC analysis. Preparative GLC produced the more rapidly eluted fraction as a colourless oil (0·2 g). The NMR spectrum of which showed it to be the saturated ketone **2c**; ν_{max} 1710 cm^{-1}. The second component had no OMe signal in the NMR spectrum, and had ν_{max} 1710 cm^{-1}. It was considered to be a product of ring-opening and hydrogenation.[cf 2a]

1-Methoxy-2-endo-(1-hydroxyethyl)bicyclo[2.2.2]*oct-5-ene* (**6**)

Reduction of the *endo*- **1h** (5 g) with LAH gave **6**; (4 g; 80%) as an oil. GLC analysis on PEGA, PEGS, and capillary GLC on PEGS showed only one component. NMR analysis showed only a single OMe signal. The *tosylate* was obtained as an oil, which showed only a single OMe signal. On standing at 0°, crystals were deposited and separated The residue was a semicrystalline oil which showed only a single OMe signal in the NMR spectrum.

1-Methoxy-2-exo-(1-hydroxyethyl)bicyclo[2.2.2]*oct-5-enes* (**7** and **8**)

The *exo* **2** (2·5 g) was reduced with LAH in ether to a mixture of **7** and **8** (2 g; 80%) in the ratio of 1:1·7. Small samples of the pure alcohols were separated by preparative GLC at 190°. The *mixed* tosylates and the *pure* tosylates were obtained, free from the parent alcohols as judged by NMR analysis of the methoxyl region, but could not be induced to crystallise.

1-Methoxy-2-(1-hydroxyethyl)bicyclo[2.2.2]*octanes* **9** *and* **10**)

The saturated ketone **2c** (0·2 g) was reduced to a mixture of **9** and **10** (0·15 g; 75%) in the ratio of 1:1·6 as shown by analysis of the OMe region of the NMR spectrum. The low field OMe was assumed to be associated with the diastereoisomer capable of intramolecular H-bonding. The alcohols were not separable on GLC. The mixed *tosylates* were obtained as a non-crystallizable oil.

1-Methoxybicyclo[2.2.2]*oct-5-en-2-one* (**13a**)

1,3-Dimethoxy-2,5-dihydrobenzene (26·7 g) was added dropwise to an ice-cooled soln of maleic anhydride (21·7 g) in dry benzene (500 ml) containing glass-wool. The mixture was allowed to warm up and then refluxed for 45 min. Removal of the solvent yielded a semi-solid mass of the crude adduct **11a** which was not further purified before reaction.

Crystallization from diethyl ether yielded the adduct as a pale yellow, microcrystalline solid; m.p. 126–128°. The IR spectrum showed bands at ν_{max} 1850 and 1780 cm^{-1}. The NMR spectrum (Table 2) was entirely in accord with the structure assigned.

The crude adduct **11a** (55 g) was dissolved in a mixture of water and DME (4:1; 400 ml) and refluxed overnight. The solvents were removed by means of a rotary evaporator to yield a viscous mass which on tritaration with acetone yielded the *keto-diacid* **12a** (22·7 g). Recrystallization from acetone gave a white crystalline powder; m.p. 182–185·5°. The yield of this compound from resorcinol dimethyl ether, was 49%.

The diacid **12a** (8·12 g) was dissolved in dry pyridine (8 ml) and O_2 was bubbled through the soln for 20 min. Recrystallized lead tetraacetate (24·2 g) was added, and the reaction vessel rapidly immersed in an oil bath at 67°. The mixture was maintained at this temp with vigorous agitation, for 7 min. After cooling, the mixture was poured into 2N HNO_3 and extracted with ether, the extracts being washed with $NaHCO_3$ aq and water. Removal of solvent gave **13a** (1·759 g) as a colourless oil, which gave a single peak on GLC analysis. The IR spectrum showed peaks at 1604 and 1728 cm^{-1}. The UV spectrum had λ_{max} 280 nm ε_{max} ~250. The NME spectrum was in accord with the structure assigned (Table 2).

1-Methoxy-3-methylbicyclo[2.2.2]*oct-5-en-2-ones* (**13b** *and* **13c**)

2-Methyl-1,3-dimethoxybenzene (8 g) in DME (50 ml) was added to liquid ammonia (1 l.). Li (15 g) in small pieces, was added over 30 min and the mixture stirred for a further 2 hr. MeOH was added to destroy the colour, and then brine added and the ammonia allowed to evaporate. Extraction with ether gave a product (7 g) containing 90% of 1,3-*dimethoxy-2-methyl-2,5-dihydrobenzene* as indicated by GLC analysis. The NMR spectrum of the product (Table 2) was in accord with this structure.

The crude product was dissolved in dry benzene (50 ml) containing glass wool, and maleic anhydride (6 g) added at room temp. After refluxing for 16 hr, the solvents were removed, and the products dissolved in dry CCl_4. Insoluble material was removed by filtration and the filtrate evaporated to give the crude adduct **11b** (10 g). The NMR spectrum (Table 2) was in accord with the proposed structure and indicated the presence of maleic anhydride (20%) and 2-methyl-1,3-dimethoxybenzene (10%).

The crude adduct was dissolved in DME : water (3 : 1 ; 600 ml) and refluxed for 16 hr. The soln was evaporated to a small volume, and extracted with large quantities of ether. Evaporation gave a solid which was washed several times with light petroleum (b.p. 40–60°) to remove aromatic impurities, and the resultant white solid recrystallized from acetone : water (1 : 1); m.p. 151–153°. This acid **12b** (6 g) had a NMR spectrum indicating the presence of a single isomer (Table 2).

Lead tetraacetate oxidation of **12b** (6 g) as above gave the *ketone* **13b** (0·9 g), shown by NMR to be a single epimer.

Equilibrium of **13b** (0·5 g) by refluxing with 10% NaOMe soln in MeOH (25 ml) for 30 min gave a mixture of **13b** and **13c** (0·45 g) which could not be resolved by GLC analysis. The NMR spectrum (Table 2) indicated the presence of 55% of the 3-*endo*methyl ketone (**13c**).

Dimethyl 7-methoxytetralin-5,6-dicarboxylate (**16**)

(a) 6-Methoxy-1,2,3,4,5,8-hexahydronaphthalene (6 g) was equilibrated with potassamide in liquid ammonia, and allowed to stand at 0° with dimethyl acetylene dicarboxylate (2·5 ml) for 12 hr. Elution with light petroleum from a short silica gel column gave first, 6-methoxytetralin, and then an oil (1·8 g) having ν_{max} 1730 cm^{-1}. This material, believed to be **15**, on warming to 140°, frothed and then solidifed on cooling The solid, on recrystallization from petrol gave white needles of the aromatic diester **16**; ν_{max} 1730 cm^{-1}; m.p. 98–99°. (Found: C, 64·8; H, 6·5. $C_{15}H_{18}O_5$ requires: C, 64·7; H, 6·5%).

(b) 6-Methoxy-1,2,3,4,5,8-hexahydronaphthalene (6 g) was mixed with dimethylacetylene dicarboxylate (6 ml) and heated in a sealed tube, under N_2, at 150° for 24 hr. On removal of volatile materials, the residue was recrystallized from petrol to give the aromatic diester **16**, m.p. 98–99° (7 g).

Hydrolysis of the diester, followed by acidification gave the corresponding anhydride **17**, m.p. 176–178°; ν_{max} 1770 and 1830 cm^{-1}. (Found: C, 67·1; H, 5·4. $C_{13}H_{12}O_4$ requires: C, 67·2; H, 5·2%).

1,4-Dihydro-2-methoxybenzoic acid (**22**)[22]

To a stirred soln of *o*-anisic acid (1·02 g) in MeOH (13 ml) and DME (5 ml) was added liquid ammonia (20 ml), and Na (0·75 g) in small pieces over 3 min. Ammonium chloride (3·1 g) was added and the ammonia allowed to evaporate. The liquid was then cooled to −5° and acidified with iced HCl (10%) to pH2. Extraction with ether yielded an oil (1·12 g) which slowly crystallized when stored at 0° under N_2. The NMR spectrum showed signals at δ 9·45 (CO, H); 5·75 (2 vinyl protons); 4·75 (1 vinyl proton); 3·5 (O-Me) and 3·66 ppm (1 methine).

1,4-Dihydrobenzoic acid

Benzoic acid (10 g) was reduced by the method of Kuehne and Lambert[23] to give a semicrystalline product, the NMR spectrum of which revealed the presence of ~25% benzoic acid.

6-Methoxytetralin-7-carboxylic acid (**24a**)

(a) To a stirred mixture of 6-methoxytetralin (41·7 g), nitrobenzene (338 g) and acetyl chloride (46·4 g) at 0° was added $AlCl_3$ (82 g) in small portions over 30 min. The soln was stirred at 0° for 5 hr, allowed to stand at 5° for 48 hr, and then poured onto ice and conc HCl (140 ml) added. The nitrobenzene was removed by steam-distillation and the residue extracted with ether. The ethereal extract was washed with water and then boiled with animal charcoal for 2 hr, before evaporation. The product was distilled to give *7-acetyl-6-methoxytetralin* **23a** (37·3 g; 72%); b.p. 110°/0·75 mm; m.p. (ex light petroleum), 43–44°, (Found: C, 76·60; H, 8·00. $C_{13}H_{16}O_2$ requires: C, 76·44; H, 7·90%). The 2,4-dinitrophenylhydrazone had m.p. 208°. (Found: C, 59·67; H, 5·58; N, 14·24. $C_{19}H_{20}O_5N_4$ requires: C, 59·37; H, 5·24; N, 14·58).

The ketone **23a** (22·8 g) was dissolved in dioxan (30 ml) and 10% NaOCl aq (40 ml) and NaOH (40 g) added. The mixture was stirred and heated under reflux for 12 hr. $NaHSO_3$ aq was added until the mixture no longer liberated I_2 from acidified KI soln and the mixture made acid to Congo Red with 50% H_2SO_4 aq. Ether extraction, followed by separation of the acidic and non-acidic components gave starting material (12 g) and the required **24a** (5 g). The acid had m.p. 115–116° (Lit.[13] 115°). An attempt to improve this reaction by using a much larger excess of hypochlorite soln gave an acid melting at 162–163° (ex CCl_4). NMR spectral analysis identified this compound as *5-chloro-6-methoxytetralin-7-carboxylic acid* **24b**. (Found: C, 59·88; H, 5·54; Cl, 14·73. $C_{12}H_{13}O_3Cl$ requires: C, 59·86; H, 5·24; Cl, 14·79%).

(b) 6-Hydroxytetralin (24 g) were dissolved in CS_2 (200 ml) and cooled to 0°. Chloracetyl chloride (24 ml) was added, and then powdered anhyd $AlCl_3$ (100 g) was added with stirring during 40 min. The mixture was maintained at 0° for 2 hr and then allowed to reach room temp, and poured onto ice. The organic layer was separated, and the aqueous layer extracted with ether and the combined organic layers washed with $NaHCO_3$ aq and water. Evaporation yielded an orange solid which was recrystallized from CCl_4 as a pale yellow solid; (**23b**; 26 g; ~70%). It had m.p. 103–104°; ν_{max} (hexachlorobutudiene) 1645 (C=O) and 3100 (broad; bonded-OH); λ_{max} 273 nm (ε_{max} 12,600) and 348 nm (ε_{max} 4320).

The chloroketone **23b** (5·02 g) was added to pyridine (5 ml) and heated under reflux, for 45 min. The brown mass was broken up, a further 2 ml pyridine added and refluxing continued for 25 min. 50% NaOH aq (7 ml) was added and the mixture refluxed for 20 min, cooled and extracted with ether. The aqueous layer was made acid to Congo Red with conc HCl, and the crude product filtered and dried in the air and by distillation from it of benzene. Recrystallization from chloroform gave the *hydroxy-acid* **24c** (2·62 g; 63%) as white flaky crystals; m.p. 177–178°.

The hydroxy acid **24c** (13 g) was disolved in an NaOH aq (14 g in 120 ml), and Me_2SO_4 (28 ml) added at room temp. After 45 min under reflux a further 5 g of NaOH in 30 ml water, and $MeSO_4$ (18 ml) were added and refluxing continued. The mixture was cooled, and water added to dissolve the precipitated salts. Extraction with ether yielded the *methyl ester* of the *methoxy-acid* (**24a**; 3·25 g; 30%). Acidification of the aqueous layer, followed by extraction with ether gave the *methoxy-acid* (**24a**; 6·92 g; 50%); m.p. 115–116°.

The methyl ester, on hydrolysis with methanolic NaOH aq yielded the acid in 95% yield.

7-Methoxy-1,2,3,4,6,9-hexahydronaphthalene-6-carboxylic acid (**21**)

To a stirred soln of **24a** (1 g) in THF (20 ml) was added liquid ammonia (40 ml) and t-butanol (15 ml). Na (0·8 g) was added in small pieces over 15 min. Ammonium chloride (2·8 g) was added, and the ammonia allowed to evaporate for 2 hours. Ice water and salt were added to reduce the temp to −3°, and the soln was acidified with 10% HCl to pH2. The mixture was extracted with $CHCl_3$, and the extract washed thoroughly with Na_2CO_3 aq. The aqueous carbonate extracts were acidified with chilled 10% HCl, and extracted with $CHCl_3$. Evaporation yielded an oil which crystallized on standing. Recrystallization from ether/n-hexane gave the *acid* **21** (0·9 g); m.p. 119–120°. The UV spectrum showed only very weak absorption at 243 nm, corresponding to less than 4% starting material. (Found: C, 69·47; H, 7·76. $C_{12}H_{15}O_3$ requires: C, 69·20; H, 7·73%).

Attempted acid-catalysed hydrolysis of 1,4-*dihydro-o-anisic acid* (**22**)

The dihydro acid (1 g), 50% HCl (2 ml) and sufficient DME to effect soln were mixed together and maintained at 60° for ½ hr. The mixture was poured into an excess Na_3CO_3 aq and extracted with ether to give after evaporation a liquid (0·5 g) having ν_{max} 3500, 1710 and 1680 cm^{-1}. Treatment with Brady's reagent gave the 2,4-dinitrophenylhydrazone of cyclohex-2-enone; m.p. 166°, in poor yield.

1-*Methoxybicyclo*[2.2.2]*oct-5-en-2-carboxylic acids* (**1a** *and* **1b**) *from* 1,4-*dihydro-o-anisic acid*

Crystalline 1,4-dihydro-*o*-anisic acid (630 mg), ethyl acrylate (3 ml) and hydroquinone (90 mg) were heated together, under N_2 to 200° in a sealed tube for 32 hr. The volatile materials were removed and the residue distilled to give an oil (210 mg), GLC analysis of which showed it to contain the Et ester of **1a** and **1b**. Hydrolysis with ethanolic KOH followed by chromatography on silica gel yielded the acids, identical with authentic samples.

Pyrolysis and Diels–Alder reaction of the hexalin-acid (**21**)

The crystalline acid **21** (460 mg), methyl acrylate (2 ml) and hydroquinone (30 mg) were heated under N_2 in a sealed tube for 36 hr at 200°. Removal of the volatile materials was followed by distillation to give

a colourless oil (340 mg). GLC analysis revealed the presence of two main components (**26a** and **26b** methyl esters). The NMR spectrum supported this structural assignment (Table 2).

Hydrolysis with ethanolic KOH gave a mixture of the acids which was subjected to chromatography on silica gel Ether/light petroleum (1:5), eluted first the *exo*-acid **26b** (30 mg); m.p. 122–123°. Further elution gave samples increasing rich in the epimeric acid **26a**, the purest sample obtained containing >80% of this isomer as judged by GLC and NMR analysis of the methyl esters, formed by reaction with diazomethane.

Hydrogenation of the unsaturated acids (**26a** *and* **26b**)

The acids, as their Me esters, were separately hydrogenated under atm press in MeOH, over Adams' catalyst. The products were obtained as colourless oils; ν_{max} 1730 cm^{-1}. The Me ester of **26a** gave the Me ester of **28a** in ~85% purity (GLC analysis). This was identical, on GLC analysis with one of the two products of hydrogenation of the Me ester of **29a**. The Me ester of **26b** gave the Me ester of **28b**, exhibiting a single peak on GLC analysis, inseparable from the product of epimerization of **28a**.

Epimerization of the methyl esters

The Me esters of **26**, **28**, **29** and **30** were epimerized by the following procedure.

The ester (20 mg) was dissolved in a sat soln of *t*-BuOK in *t*-BuOH (1 ml) in an ignition tube. The tube was chilled, flushed out with dry N_2, sealed and maintained at 100° for 48 hr. Solvent was removed in a rotary evaporator, the residue acidified and extracted with ether. Esterification with ethereal diazomethane was followed by GLC analysis.

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