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THE DIRECTING EFFECT OF ANNELATED RINGS IN AROMATIC SYSTEMS—II

SYNTHESIS AND OXIDATION OF 2,3-DIHYDRO-5-BENZOFURANOLS–I. AN APPARENT MILLS–NIXON EFFECT IN OXIDATIVE COUPLING OF PHENOLS*†

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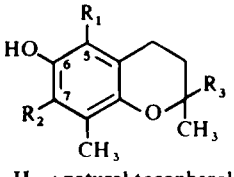
Abstract—2,3-Dihydro-5-benzofuranols related to β- and γ-tocopherol and to tocol have been synthesized and their oxidation with alkaline ferricyanide has been studied. Oxidation of 2,3-dihydro-2,2-dimethyl-5-benzofuranol gave a spiroketal trimer **10** by C—C and C—O coupling *via* the 6-position of the molecule. This indicates a directing effect on the oxidative coupling by the annelated 5-membered heterocyclic ring which is in accord with the predictions based on the Mills–Nixon effect. Similar oxidation of 2,3-dihydro-2,2,4,7-tetramethyl-5-benzofuranol and of 2,3-dihydro-2,2,6,7-tetramethyl-5-benzofuranol (analogues of β- and γ-tocopherol, respectively) gave the hydroxyquinones **11** and **12** by reactions involving opening of the heterocyclic ring.

IN THIS paper we present results that demonstrate an apparent Mills–Nixon effect in the oxidative coupling of 2,3-dihydro-2,2-dimethyl-5-benzofuranol. The data also indicate that the directing effect of an annelated heterocyclic ring containing oxygen is stronger than that of the corresponding alicyclic ring.

The oxidation of tocopherols (**1a–4a**) and of their model compounds (**1b–4b**) has been studied by a number of workers using alkaline ferricyanide as oxidizing agent.[1] Depending on the structure of the tocopherol, two types of coupling products are formed. If the chromanol moiety of the molecule has an unsubstituted 5-position, as in γ- and δ-tocopherol (**3** and **4**), the main oxidation product is an unstable spiroketal



a: $R_3 = C_{16}H_{33}$; natural tocopherol

b: $R_3 = CH_3$; tocopherol model compound

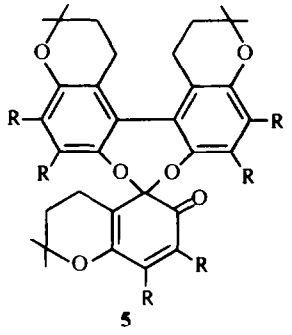
	R_1	R_2	
1	CH_3	CH_3	α-tocopherol
2	CH_3	H	β-tocopherol
3	H	CH_3	γ-tocopherol
4	H	H	δ-tocopherol

trimer of type **5** formed by C—C and C—O coupling involving only the 5-positions. If the chromanol has a Me group in the 5-position, as in α- and β-tocopherol (**1** and **2**), benzylic coupling occurs *via* this Me group and the main product is a spiro dimer of

* Part 1 in this series see Ref. 9.

† The designation "Mills–Nixon effect" in this paper is used to indicate a preference for reaction at one of the two possible positions *ortho* to the OH group in the phenols studied. No implication concerning the mechanism behind this preference is made.

type **6**. This spiro dimer is formed even if the other position *ortho* to the OH group (the 7-position) is unsubstituted thus demonstrating a strong preference for oxidative coupling at the 5-position in 6-chromanols. This reaction pattern has been elucidated



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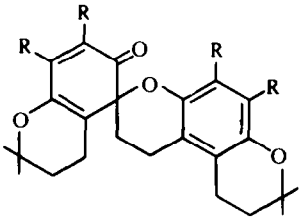
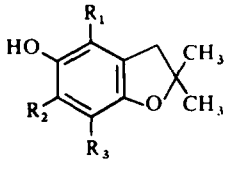


6: R = Me or H

using the tocopherol model compounds **1b–4b** and other related chromanols[2] and the work has recently been reviewed.[3]

The directing effect of annelated rings in electrophilic aromatic substitution has been demonstrated in a number of cases since it was first discovered by Mills and Nixon in 1930.[4] The phenomenon has later been referred to as the "Mills–Nixon effect", and much of the early experimental work has been reviewed by Berthier and Pullman.[5] In the original work[4] it was demonstrated that substitution of 6-hydroxytetralin occurred preferentially at the 5-position and that 5-hydroxyindane under similar conditions reacted mainly at the 6-position. Subsequent work has shown that 6-chromanol[6, 7] and 2,3-dihydro-5-benzofuranol[8] also undergo electrophilic substitution according to the pattern predicted by the Mills–Nixon effect. In our study of tocopherol chemistry[3] we showed that a Mills–Nixon effect can appear also in oxidative coupling reactions, which in this case take place almost exclusively at the 5-positions. We were later unable to demonstrate a similar effect in the oxidative coupling of various 5-hydroxyindanes and 6-hydroxytetralins.[9] Apart from these investigations, apparently no work has been done to show a Mills–Nixon effect in oxidative coupling of phenols.

As part of our current program to study the directing effect of various annelated rings in aromatic systems we have now examined the oxidative coupling of the 5-benzofuranols **7–9**. These compounds are analogues of the chromanols[2] a 5-



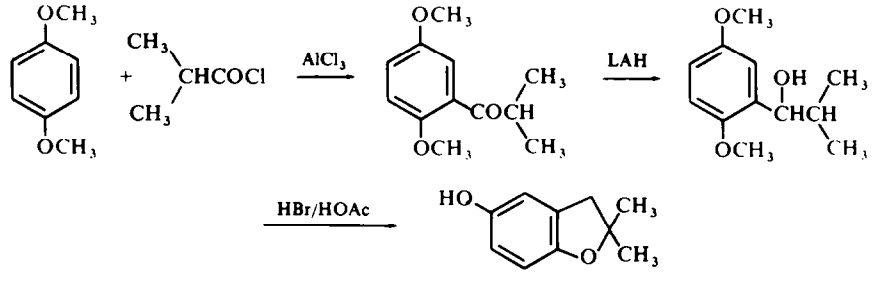
	R_1	R_2	R_3
7	H	H	H
8	CH_3	H	CH_3
9	H	CH_3	CH_3

membered heterocyclic ring taking the place of the 6-membered ring in the latter compounds. A possible Mills–Nixon effect would thus manifest itself as a preference for coupling at position 6. Further, if the phenols **7–9** reacted like the 6-chromanols, products of type **5** could be expected from **7** and **8** while **9** would form a spiro dimer of type **6**.

Synthetic procedures

In the preparation of the 2,3-dihydro-5-benzofuranols (**7–9**) we tried three different routes, as shown in Schemes 1–3. Preparation of **7** was carried out as shown in Scheme 1. The hydroquinone dimethylether was condensed in a Friedel–Craft reaction with isobutyryl chloride and the ketone formed was reduced to the corresponding alcohol, which gave **7** upon treatment with HBr in acetic acid. This last step apparently involves demethylation to the free hydroquinone, water elimination from the side-chain and final ring closure to the dihydrobenzofuranol. When the same route was attempted for the preparation of **8** and **9** very poor yields (< 10%) were obtained in the Friedel–Craft reaction. We therefore developed two other procedures, both more convenient than the first route. As shown in Scheme 2, 2,5-dimethyoxy-3,5-dimethylbenzaldehyde was reacted with isopropyl magnesium bromide to give a secondary alcohol which was converted to **8** using HBr as before.

SCHEME 1



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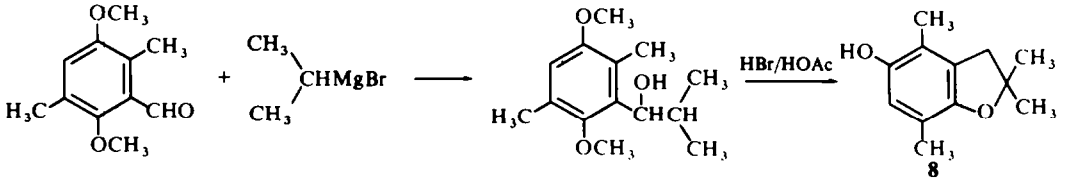
SCHEME 2



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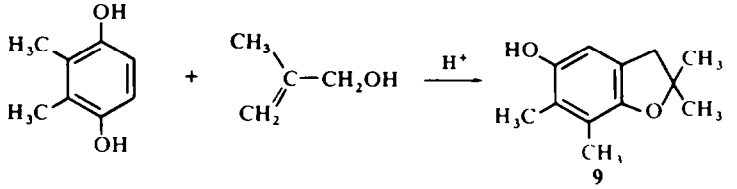
SCHEME 3



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By the third procedure, which is related to a method used for the preparation of tocopherol model compounds (**1b–4b**),[2] the dihydrobenzofuranol **9** was obtained in a one-step synthesis (Scheme 3). A solution of 2,3-dimethylhydroquinone and 2-methylallyl alcohol in anhydrous formic acid was refluxed in the presence of a catalytic amount of sulphuric acid. From this reaction the phenol **9** was obtained in 29% yield. The dihydrobenzofuranols **7** and **8** were later prepared by this method in comparable yields.

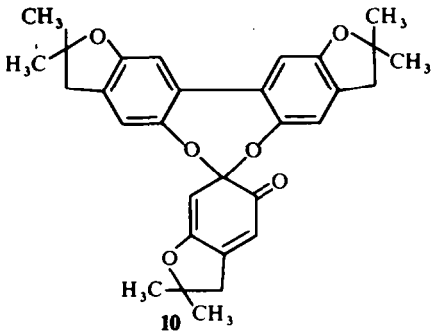
Oxidation reactions and results

As oxidizing agent we used alkaline ferricyanide, which has previously been used to study tocopherol oxidation.[1] The reactions were carried out in 2-phase systems as previously described:[1] an aqueous alkaline solution of potassium ferricyanide was rapidly stirred with an ethereal solution of the benzofuranol and the products were isolated by preparative TLC.

In the oxidation of 2,3-dihydro-2,2-dimethyl-5-benzofuranol (**7**), the organic layer assumed a transitory deep blue colour. A similar phenomenon has been reported by Hewgill[10] in the oxidation of other *p*-alkoxyphenols with alkaline ferricyanide, and was also observed by us[1] in the oxidation of tocopherol model compounds unsubstituted at position 5. After 30 min, the colour turned brown and a yellow oil was eventually isolated (60% yield) by preparative TLC. The mol. wt. of this product was determined to 440, indicating a trimer (calc mol. wt. 486). The UV spectrum showed λ_{max} (hexane) 312 nm and the IR spectrum, which has no OH absorption, exhibits two bands at 1630 and 1680 cm^{-1} indicating an unsaturated ketone.[11] The latter band appears as a finely split doublet (1675 and 1685 cm^{-1}). The NMR spectrum gave conclusive evidence for structure **10**. It shows a singlet at τ 3·24 representing four aromatic protons. Vinylic protons appear at τ 3·98 (t,1H, $J \sim 2$ cs) and 4·47 (s,1H). Protons from the heterocyclic ring give rise to a singlet at τ 7·00 (4H) and a doublet centered at τ 7·20 (2H, $J \sim 2$ cs), and the geminal Me groups appear as two singlets at τ 8·54 and 8·59 (altogether 18H). These data are consistent with structure **10**, a spiroketal trimer analogous to the trimers formed under the same conditions from 6-chromanols unsubstituted at position 5.[1] Similar trimers were obtained by Hewgill[10] in the oxidation of *p*-alkoxyphenols. The triplet at τ 3·98 in the NMR spectrum is apparently due to the vinylic proton in the α-position to the CO group in the cyclohexadienon ring. The methylene protons in the adjacent 5-membered heterocyclic ring appear as a doublet at τ 7·20 and are long-range coupled to the vinylic protons. This demonstrates that the trimer is formed by coupling at the 6-position, which is in accord with the predictions based on the Mills–Nixon effect. A number of other products formed in low yield were not further investigated.

The course of oxidation of 2,3-dihydro-2,2,4,7-tetramethyl-5-benzofuranol (**8**) and of 2,3-dihydro-2,2,6,7-tetramethyl-5-benzofuranol (**9**) (homologs of β- and γ-tocopherol model compounds, **2b** and **3b** respectively) was different than that of the corresponding chromanols and of unsubstituted dihydrobenzofuranol **7**. When compound **8** was treated with alkaline ferricyanide, no blue colour was observed in the organic layer, and the main product (30% yield) was a red oil, more polar than the starting material (R_f 0·17 and 0·55 on silica gel G in ether : light petroleum 2 : 3). The chromatogram showed a positive reaction when sprayed with leucomethylene blue, indicating a quinone, and the mass spectrum gave a mol. wt. of 208 as evidenced by the appearance of typical M and M + 2 parent ion cluster.[12]

The UV spectrum exhibits λ_{max} (hexane) 259 nm and the IR spectrum shows an OH absorption at 3450 cm^{-1} and a CO absorption at 1640 cm^{-1}. These data together with the NMR spectrum give conclusive evidence for structure **11**, a hydroxyquinone formed by opening of the 5-membered ring. In the NMR spectrum, the ring proton appears as a quartet centered at τ 3·40 ($J \sim 2$ cs) and coupled with the adjacent ring Me group, which appears as a doublet centered at τ 7·93 ($J \sim 2$ cs). The latter is partly overlapped by the signal due to the other ring Me group, which is a singlet at



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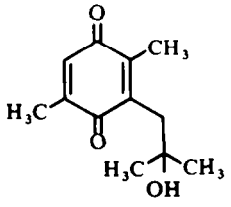

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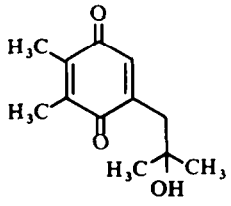

12

τ 7·90. The aliphatic methylene protons in the side chain appear as a singlet at τ 7·20 and the geminal Me groups give a singlet at τ 8·76.

A number of other products were formed and isolated in low yield. Their IR spectra indicate that none of them had the spiroketal trimer structure similar to **10** or the spiro dimer structure of type **6**. The compounds were not further investigated.

Oxidation of **9** also gave a hydroxyquinone as the major product (25% yield), identified as **12** by its spectral data, presented in the Table.

DISCUSSION OF THE RESULTS

As mentioned above, 5-indanol,[4] 2,3-dihydro-5-benzofuranol,[8] 6-hydroxytetralin[4] and 6-chromanol[6,7] all show a Mills–Nixon effect in electrophilic substitution reactions. The first two compounds preferentially react at position 6 while the last two react at position 5. In oxidative coupling reactions of 5-indanol and 6-hydroxytetralin, with or without aromatic Me groups, we were unable to demonstrate a preference for coupling at one of the two positions *ortho* to the OH group.[9] This would indicate a weak or non-existent Mills–Nixon effect in oxidative coupling of phenols with alicyclic 5- or 6-membered annelated rings. However, in the oxidation of chromanols related to tocopherols[2] (compounds with a 6-membered annelated heterocyclic ring containing oxygen) a pronounced preference for reaction at the 5-position is shown. This effect is so dominating that a 6-chromanol with a Me group at position 5 and with the 7-position unsubstituted (e.g. β-tocopherol **2**) forms products by benzylic type coupling *via* the 5-Me group and only negligible reaction occurs at the free 7-position. In the 2,3-dihydro-5-benzofuranols studied here, a preference for oxidative coupling at the 6-position is observed in the oxidation of compound **7**, while a reaction to hydroxyquinones by opening of the heterocyclic ring is dominating

TABLE 1. PHYSICAL CONSTANTS FOR OXIDATION PRODUCTS OF 2,3-DIHYDRO-5-BENZOFURANOL

Compound	Formula	Yield %	UV λ_{max}^{hexane} (nm)	IR film (cm^{-1})	NMR τ-units[a]				MS m/e/intensity %
					Aromatic	Methylene protons	Ring methyl groups	Geminal methyl groups	
10	$C_{30}H_{30}O_6$	60	312	1630 1680[b]	3·24 (s,4)	7·00[c] (s,4) 7·20 (d,2)		8·54 8·59 (Together 18H)	
11	$C_{12}H_{16}O_3$	30	259	3450 1645	3·40 (q,1)	7·20 (s,2)	7·93 (d,3) 7·90 (s,3)	8·76 (s,6)	208 and 210/1 (M and M +2)[e] 151/22 150/100 122/70 107/28
12	$C_{12}H_{16}O_3$	25	259	3450 1645	3·37 (s,1)	7·36 (s,2)	7·96 (s,6)	8·76 (s,6)	208 and 210/1 (M and M +2)[e] 151/30 150/100 122/53 107/18

[a] Sample in $CDCl_3$ soln.
[b] This band is a finely split doublet with peaks at 1685 and 1675 cm^{-1}.
[c] Vinylic protons at τ 3·98 (t, 1H, $J \sim 2$ cs) and 4·47 (s, 1H).
[d] Molecular weight was determined to 440 (calc 486) by the apparatus described.
[e] See text and Ref 12.

for the dihydrobenzofuranols with two aromatic Me groups (**8** and **9**). Such a reaction does not take place or only to a very small extent when the corresponding chromanols are oxidized under the same conditions.[13] Quinone formation from **8** and **9** is apparently faster than the coupling reaction. Nevertheless, the structure of the spiroketal trimer **10** indicates a Mills–Nixon effect in the oxidative coupling of 2,3-dihydro-2,2-dimethyl-5-benzofuranol.

The results obtained so far seem to indicate a stronger Mills–Nixon effect in oxidative coupling of bicyclic phenols if the annelated ring contains oxygen, as in 6-chromanols and 5-benzofuranols, than when the ring is alicyclic, as in 5-indanol and 6-hydroxytetralin.

EXPERIMENTAL

General comments. IR spectra were measured on a Perkin–Elmer 237 spectrophotometer, and UV absorptions were measured on a Bausch & Lomb Spectronic 505 spectrophotometer. NMR spectra were measured with a Varian Associates A 60 instrument, using $CDCl_3$ solns. Chemical shifts are expressed in τ-units relative to TMS. Mass spectra were obtained with a LKB 9000 instrument, electron energy level 70 eV. Mol. wts were determined with a Hitachi Perkin–Elmer model 115 Molecular Weight Apparatus using benzene as solvent. TLC was performed using silica gel G plates of 0·3 mm (analytical) and 1 mm (preparative) thickness. The plates were activated by heating at 130° for 1·5 hr and were stored in a dry cabinet until used. Redistilled light petroleum b.p. 40–60° was used throughout.

1-(2,5-*Dimethoxyphenyl*)*isobutanol* (Scheme 1). 2,5-Dimethoxyphenylisopropylketone[14] (30 g) was slowly added to LAH_4 (2·8 g) in ether (150 ml). The mixture was stirred and refluxed for 2 hr whereupon water (10 ml) was slowly added and then 5N HCl (100 ml). The mixture was extracted with ether, dried (Na_2SO_4), the solvent was evaporated and the residue was distilled, affording 27 g (90%) of the alcohol, b.p. 130–135°/1·5 mm. (Found: C, 68·3; H, 8·15. $C_{12}H_{18}O_3$ requires: C, 68·5; H, 8·63%).

2,3-*Dihydro*-2,2-*dimethyl*-5-*benzofuranol* (**7**). 1-(2,5-Dimethoxyphenyl)-isobutanol (16 g) and HBr (110 ml, 48%) in AcOH (180 ml) were refluxed for 2 hr. The soln was then poured onto ice (500 g) and extracted with ether. The ether extract was washed with water (3 × 100 ml), with satd $NaHCO_3$ aq (2 × 100 ml), dried (Na_2SO_4) and evaporated. The residual brown oil (13·5 g) was distilled, yielding 6 g (48%) of **7**, b.p. 160–162°/2 mm; m.p. 98–99° (from light petroleum). (Found: C, 73·4; H, 7·10. $C_{10}H_{12}O_2$ requires: C, 73·1; H, 7·36%); λ_{max} (hexane) = 305 and 312 nm; ν_{max} (KBr) 3350 cm^{-1} (OH); NMR τ 3·2–3·5 (m, 3H, ArH), τ 3·97 (s, 1H, OH), τ 7·05 (s, 2H, $ArCH_2$—) and τ 8·50 (s, 6H, gem-CH_3).

1-(2,5-*Dimethoxy*-3,6-*dimethylphenyl*)-*isobutanol* (Scheme 2). 2,5-Dimethoxy-3,6-dimethylbenzaldehyde[15] (3 g) in ether (100 ml) was slowly added to i-PrMgBr (from 3,7 g i-PrBr and 1·0 g Mg) in ether (50 ml) and the mixture was stirred overnight at room temp. It was then acidified with 1N HCl, the layers were separated and the ethereal layer washed with water, dried (Na_2SO_4) and evaporated. This yielded an oil (3,4 g, 92%) identified as the i-PrOH by its IR spectrum. The compound was taken to the next step without purification.

2,3-*Dihydro*-2,2,4,7-*tetramethyl*-5-*benzofuranol* (**8**). The above i-PrOH (3 g) in HBr (20 ml) and AcOH (40 ml) was refluxed for 2 hr. The mixture was worked up as described for **7** affording a dark oil that was placed on a column of silica gel (100 g). Elution with ether/light petroleum (1:1; 1000 ml) yielded 2 g of an oil that did not crystallize. A small sample was further purified by preparative TLC for analysis. The compound was less polar than 2,5-dimethylhydroquinone,[16] indicating that ring closure had taken place. (R_f 0·48 and 0·19, respectively, in ether/light petroleum 3:10). (Found: C, 74·9; H, 8·24. $C_{12}H_{16}O_2$ requires: C, 75·0; H, 8·39%); λ_{max} (hexane) = 298 and 302 (sh) nm; ν_{max} (film) 3400 cm^{-1} (OH); NMR: τ 3·61 (s, 1H, ArH), τ 5·0 (broad s, 1H, OH), τ 7·10 (s, 2H, $ArCH_2$—), τ 7·90 (s, 6H, $ArCH_3$) and τ 8·55 (s, 6H, gem-CH_3).

2,3-*Dihydro*-2,2,6,7-*tetramethyl*-5-*benzofuranol* (**9**) (Scheme 3). To 2,3-dimethylhydroquinone[16] (5 g) and 2-methylallyl alcohol (2·6 g) in anhyd formic acid (200 ml) was added two drops of conc H_2SO_4 and the soln was heated on an oil bath (100°) overnight. (In the absence of the H_2SO_4 no reaction took place.) The dark soln was poured onto crushed ice (500 g) and the soln was extracted with ether. The ether extract was washed with water (5 × 100 ml), with sat $NaHCO_3$ aq (2 × 100 ml) and evaporated. The residue was dissolved in MeOH (100 ml), conc HCl (1 ml) was added and the soln was refluxed for 15 min to hydrolyze formate esters. After evaporation of solvent, the residue was treated with ether/light petroleum 1:9. This precipitated unreacted hydroquinone and dissolved the benzofuranol. After filtration and evaporation of the solvent, 4 g of a dark solid material was obtained which was recrystallized from light petroleum to give

2 g (29%) of tan coloured crystals m.p. 102–104°. Further crystallization from EtOH/water raised the m.p. to 106–108°. The compound was less polar on TLC than the parent hydroquinone. (R_f 0·45 and 0·19, respectively, in ether/light petroleum 3:10). (Found: C, 75·0; H, 8·29. $C_{12}H_{16}O_2$ requires: C, 75·0; H, 8·39%); λ_{max} (hexane) = 298 and 302 (sh) nm; ν_{max} (KBr) 3400 cm^{-1} (OH); NMR: τ 3·53 (s, 1H, ArH), τ 5·50 (s, 1H, OH), τ 7·10 (s, 2H, $ArCH_2$—), τ 7·90 (s, 6H, $ArCH_3$) and τ 8·60 (s, 6H, gem-CH_3).

Oxidation procedures. The oxidation were carried out as previously described[1] for the β-tocopherol model compounds **2b** using three equivalents of the oxidizing agent. The products were isolated by preparative TLC using ether/light petroleum mixtures as solvent. Several products were formed in all the oxidations, most of them in small yield. Only the structures of the main products were studied extensively. The structure of each compound described is assigned on the basis of mol. wt. determinations and its characteristic spectral properties (Table).

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