245. *Griseofulvin Analogues. Part V.* Infrared Absorption.*

By J. E. PAGE and SUSAN E. STANIFORTH.

The infrared absorptions of 141 analogues of griseofulvin and isogriseofulvin have been examined, and the behaviour of absorption bands associated with carbonyl, alkyl, alkoxy-, alkylthio-, and halogen substituents is described. Absorption bands that can be used to distinguish between 4′-oxo-2′-enol ether and 2′-oxo-4′-enol ether analogues, and between griseofulvin and epigriseofulvin, are reported. Certain analogies with the spectra of 1-methoxycholest-1-en-3-one and 3-methoxycholest-2-en-1-one are discussed.

ALTHOUGH infrared absorption spectra of Nujol mulls of griseofulvin and several griseofulvin derivatives have been reported previously,[1] the detailed interpretation of the spectra has not been attempted. We have examined under standard conditions the infrared spectra of 141 griseofulvin analogues and here suggest structural assignments for their principal absorption bands. The griseofulvin analogues, which had been prepared in these laboratories during a study of the effect of structural change on antifungal activity,[2] contain various alkyl, alkoxy-, alkylthio-, and halogen substituents at different positions

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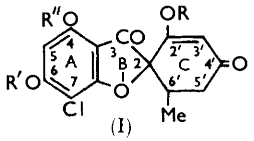
* Part IV, preceding paper.

[1] (*a*) Grove, MacMillan, Mulholland, and Rogers, *J.*, 1952, 3949; Mulholland, *J.*, 1952, (*b*) 3987, (*c*) 3994; (*d*) Duncanson, Grove, MacMillan, and Mulholland, *J.*, 1957, 3555; (*e*) Brossi, Baumann, Gerecke, and Kyburz, *Helv. Chim. Acta*, 1960, **43**, 2071.

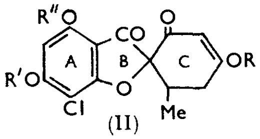
[2] (*a*) Arkley, Attenburrow, Gregory, and Walker, *J.*, 1962, 1260; (*b*) Gregory, Holton, Robinson, and Walker, *J.*, 1962, 1269; (*c*) Walker, Warburton, and Webb, *J.*, 1962, 1277; (*d*) Stephenson, Walker, Warburton, and Webb, preceding paper.

on a rigid ring system of known configuration.[3] The infrared spectra of the steroid isomers, 1-methoxycholest-1-en-3-one and 3-methoxycholest-2-en-1-one,[4] in which the steroid ring-A substitution patterns are similar to those in ring-C of griseofulvin (I; $R = R' = R'' = Me$) and isogriseofulvin (II; $R = R' = R'' = Me$), respectively, will also be considered.

Bromoform solution spectra were studied, since in solution spectra, as compared with Nujol mull or potassium bromide disc spectra, intermolecular hydrogen-bonding effects are largely eliminated; bromoform is a better solvent than carbon disulphide or carbon tetrachloride for griseofulvin and its analogues and it transmits over a slightly wider and more useful spectral region than does chloroform. The Nujol mull spectra of all the griseofulvin analogues were recorded, but they are not discussed in detail.



(I)



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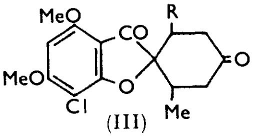

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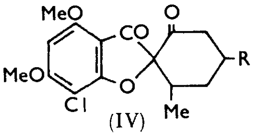

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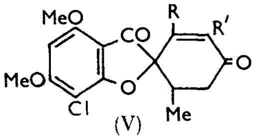

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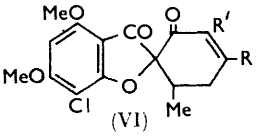

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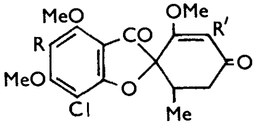

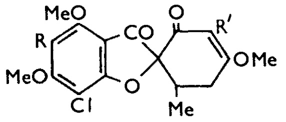

(VIII)

Carbonyl Stretching Bands.—Bromoform solution spectra of griseofulvin and isogriseofulvin (Table 1) show strong absorption bands in the C=O and C=C stretching regions at 1705, 1654, 1615, and 1591, and at 1698, 1660, and 1614—1598 cm.$^{-1}$, respectively. The bands between 1615 and 1590 cm.$^{-1}$, which would normally be assigned to C=C stretching, are, rather surprisingly, about three times as strong as those between 1710 and 1650 cm.$^{-1}$, which would be assigned to C=O stretching; carbonyl bands are usually at least five times as strong as C=C bands. We therefore examined the behaviour of the bands in different solvents (see Bellamy and Williams [5]).

The results listed in Table 2, in which the conventions used by Bellamy and Williams are followed, show that the 1705 and 1654 cm.$^{-1}$ bands for griseofulvin are more sensitive than the 1615 and 1591 cm.$^{-1}$ bands to solvent changes. Since C=O groups are more polar and consequently show larger displacements than C=C bands in different solvents, we believe that the 1705 and 1654 cm.$^{-1}$ bands are associated with the 3- and 4'-ketones, respectively, and the 1615 and 1591 cm.$^{-1}$ bands with various C=C linkages. Similar results were obtained for isogriseofulvin.

The position and relative intensities of the carbonyl bands can be used to distinguish between, and to determine in the presence of each other, griseofulvin and isogriseofulvin. In griseofulvin, the 3-ketone band (1705 cm.$^{-1}$) appears about 50 cm.$^{-1}$ higher and is more intense (apparent $\varepsilon \sim 760$) than the 4'-ketone band (apparent $\varepsilon \sim 500$), whereas in isogriseofulvin, the 3-ketone band (1698 cm.$^{-1}$) is only 38 cm.$^{-1}$ higher and is less intense (apparent $\varepsilon \sim 600$) than the 2'-ketone band (apparent $\varepsilon \sim 700$).

Of the steroid isomers, 1-methoxycholest-1-en-3-one and 3-methoxycholest-2-en-1-one,

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[3] MacMillan, *J.*, 1959, 1823.

[4] Tamm, *Helv. Chim. Acta*, 1960, **43**, 1700.

[5] Bellamy and Williams, *Proc. Roy. Soc.*, 1960, *A*, **255**, 22.

TABLE 1.

Absorption bands (cm.$^{-1}$) for 4-, 6-, 2′-, and 4′-alkoxy-analogues of griseofulvin and isogriseofulvin ($CHBr_3$ solution).

Compound					C=O	C=C		
	R	R′	R″	Ref.	stretching	stretching	1490—1210	1090—730
I	Me	Me	Me	*a*	1705s 1654s	1615—1591s 1508s	1468—1462s 1438s 1416—1408s 1386m 1352s 1282w 1245m 1230—1220s	1054s 1000s 982m 966s 890m 838m 800s 775w
II	Me	Me	Me	*a*	1698s 1660s	1614—1598s 1510s	1470—1462s 1438s 1410s 1388s 1350s 1232—1222s	1068m 1010m 1000s 982m 914w 888m 842s 800s 876w
I	Et	Me	Me	*b*	1704s 1654s	1615—1592s 1508s	1468—1460s 1438s 1416—1406s 1385m 1376m 1348s 1280w 1228—1220s	1052s 1000s 976m 934w 890m 838w 818m 800s 772w
II	Et	Me	Me	*b*	1694s 1660s	1610—1594s 1508s	1468—1460s 1438s 1418—1410s 1385s 1348s 1330s 1230—1220s	1062m 1028s 1002s 978w 940m 882m 842m 820m 800s 772w
I	Pr^n	Me	Me	*c*	1706s 1652s	1618—1595s 1510s	1470—1462s 1438s 1416—1408s 1386w 1352s 1280w 1246m 1226—1220s	1058s 1036m 1000s 980m 966m 950s 910w 890s 834m 798s 776w
II	Pr^n	Me	Me	*c*	1694s 1658s	1615—1595s 1508s	1468—1460s 1438s 1416—1410s 1382—1374s 1348s 1228—1220s	1058m 1005—990s 962s 908w 884m 840s 798s 775w
I	Pr^i	Me	Me	*d*	1706s 1652s	1616—1595s 1508s	1470—1462s 1438s 1416—1408s 1385m 1366s 1350s 1280w 1228—1220s	1056s 1034s 1000s 980m 938m 902w 890m 838m 820w 798s 774w
II	Pr^i	Me	Me	*c*	1696s 1658s	1614—1592s 1508s	1470—1462s 1438s 1418m 1406—1400s 1388s 1350s 1228—1220s	1062s 1002s 980w 948s 908w 882m 840m 820m 798s 774w
I	Bu^n	Me	Me	*c*	1708s 1656s	1616—1598s 1510s	1470—1464s 1438s 1408s 1386m 1354—1350s 1282m 1248m 1228—1222s	1056—1044m 1000s 984m 952m 890m 836m 800s 776w
II	Bu^n	Me	Me	*c*	1698s 1664s	1616—1598s 1510s	1470—1464s 1438s 1412s 1380m 1352s 1230—1220s	1065m 1006s 974—965m 886w 842s 800s 778w
I	Allyl	Me	Me	*e*	1706s 1655s	1616—1595s 1508s	1468—1460s 1438s 1416—1408s 1386m 1350—1332s 1280m 1248m 1228—1220s	1055m 1042s 1000s 982m 964m 932m 890m 832m 800s 774w
II	Allyl	Me	Me	*e*	1694s 1660s	1616—1595s 1508s	1468—1460s 1438s 1420s 1408s 1400s 1388m 1350—1332s 1246m 1226—1220s	1066m 1006s 985s 936m 884m 840s 800s 774w
I	n-Hexyl	Me	Me	*c*	1706s 1654s	1616—1592s 1508s	1470—1462s 1438s 1418—1408s 1386w 1352s 1278w 1226—1220s	1056m 1000s 982m 940w 888m 832m 800s 775w
II	n-Hexyl	Me	Me	*c*	1698s 1660s	1615—1592s 1508s	1470—1462s 1438s 1410s 1378m 1352s 1230—1220s	1064m 1000s 974m 940w 882m 840s 800s 775w
I	Ph	Me	Me	*f*	1706s 1656s	1615s 1592s 1506s 1492s	1468—1460s 1438s 1416—1408s 1386w 1354—1350s 1282w 1252m 1220—1210s	1058m 1020m 1000s 978m 932w 912w 892m 852w 815w 800s 778m 768m
II	Ph	Me	Me	*f*	1698s 1664s	1616s 1592s 1506s 1490s	1468—1460s 1438s 1418—1408s 1386s 1350s 1330m 1242m 1220—1210s	1060m 1000s 975w 930m 908w 882m 850s 812w 800s 772s 736w
I	CH_2Ph	Me	Me	*e*	1706s 1652s	1616—1592s 1506s 1498w	1470—1462s 1438s 1418—1408s 1386w 1352s 1280w 1226—1220s	1052m 1032w 1000s 982m 966m 890m 835m 800s 775w 736m
II	CH_2Ph	Me	Me	*e*	1696s 1660s	1615—1592s 1506s 1498w	1468—1462s 1438s 1418—1406s 1384w 1368m 1348s 1226—1220s	1063m 1000s 973s 933w 906w 884m 840s 800s 775w 752m 736m
I	Me	Et	Me	*d*	1704s 1654s	1614—1592s 1506s	1476m 1464s 1448s 1410s 1388m 1380m 1352—1340s 1280w 1248m 1230—1215s	1086s 1054s 1020w 998s 984m 966s 922w 912m 880w 868w 836s 800s 772w

TABLE 1 (cont.)

II	Me	Et	Me	*d*	1696s 1660s	1612—1594s 1508s	1476m 1464s 1448s 1410—1400s 1390s 1350— 1338s 1230—1214s	1068s 1018m 1005m 994s 914w 885w 870w 840s 798s 774w
I	Me	Me	Et	*d*	1706s 1652s	1616—1594s 1508s	1466—1460s 1448s 1406s 1386m 1380m 1350— 1346s 1282w 1230—1218m	1056s 1208m 994m 965s 910s 838m 800s 775w
I	Et	Et	Me	*g*	1704s 1650s	1614—1592s 1508s	1478m 1465s 1448s 1410s 1388w 1378m 1350— 1340s 1282w 1230—1220s	1052s 998s 938w 920w 912m 880w 865m 840w 818m 860s 780w
II	Et	Et	Me	*g*	1698s 1660s	1614—1594s 1508s	1478m 1464s 1448s 1410s 1385s 1350—1335s 1228—1215s	1065m 1024s 1000s 940m 915w 898m 864w 842m 822m 798s 772w
I	Me	Et	Et	*h*	1706s 1652s	1616s 1592s 1506s	1474s 1462s 1442m 1416s 1398s 1380s 1358s 1336s 1280w 1228s 1205s	1050s 1022—1012m 990s 962s 922m 910w 888— 875w 830s 790s 766w
II	Me	Et	Et	*h*	1698s 1662s	1616—1594s 1506s	1474s 1462s 1448m 1416s 1390—1382s 1336s 1228s 1204s	1062m 1016m 990s 918m 880w 835s 790m 766w
I	Et	Et	Et	*h*	1704s 1650s	1616—1594s 1506s	1474s 1460s 1446m 1416s 1398s 1378s 1346— 1335s 1280w 1222—1205s	1048s 1015m 988s 932m 918—910m 886w 860m 835w 821m 790s 766w
II	Et	Et	Et	*h*	1698s 1660s	1615—1600s 1506s	1474s 1460s 1446m 1416s 1398m 1386s 1364m 1335s 1226—1206s	1062m 1020s 990s 935m 915m 882w 860w 836m 815m 790s 766w

The following analogues (ref. *d*) were also examined: (I; R = R″ = Me, R′ = Pr^n, Pr^i, Bu^n, $CH_2{:}CH{\cdot}CH_2$, *n*-$C_{16}H_{33}$, or CH_2Ph); (II; R = R″ = Me, R′ = Pr^n, Pr^i, Bu^n, $CH_2{:}CH{\cdot}CH_2$, or CH_2Ph); (I; R = R′ = Me, R″ = Pr^n, Pr^i, Bu^n, $CH_2{:}CH{\cdot}CH_2$, or CH_2Ph); (I; R = R′ = Bu^n, R″ = Me); and (II; R = R′ = Bu^n, R″ = Me).

a, Ref. 1*a*. *b* Grove, MacMillan, Mulholland, and Rogers, *J.*, 1952, 3977. *c*, Duncanson, Grove, and Jeffs, *J.*, 1958, 2929. *d*, ref. 2*a*. *e*, ref. 2*b*. *f*, ref. 2*d*. *g*, ref. 1*d*. *h*, ref. 3.

TABLE 2.

Carbonyl and C=C frequencies (cm.$^{-1}$) of griseofulvin in various solvents (computed on basis of value in dioxan).

	3-Ketone		4′-Ketone		C=C		C=C	
Solvent	ν (C=O)	$10^4\Delta\nu/\nu$	ν (C=O)	$10^4\Delta\nu/\nu$	ν (C=C)	$10^4\Delta\nu/\nu$	ν (C=C)	$10^4\Delta\nu/\nu$
Et_2O	1718	−23	1670	0	1610	50	—	—
CCl_4	1714	0	1672	−12	1616	12	—	—
Dioxan	1714	0	1670	0	1618	0	1594	0
MeCN	1710	23	1667	18	1616	12	1593	6
$(CH_2Cl)_2$	1711	18	1665	30	1618	0	1593	6
CH_2Cl_2	1710	23	1662	48	1618	0	1594	0
$CHCl_3$	1709	29	1660	60	1620	−12	1596	−12
$(CHCl_2)_2$	1707	41	1658	72	1618	0	1596	−12
$CHBr_3$	1705	53	1654	96	1615	18	1591	18

the 3-ketone absorbed at a slightly lower frequency (1634 cm.$^{-1}$) than the 1-ketone (1642 cm.$^{-1}$); this displacement parallels the behaviour of the 4′- (1654 cm.$^{-1}$) and 2′-ketone (1660 cm.$^{-1}$) from griseofulvin and isogriseofulvin, respectively, but contrasts with Roberts, Gallagher, and Jones's observation[6] that a 1-oxo-steroid has a lower C=O frequency than a 3-oxo-steroid, and with our own[7] that an α-alkyl substituent tends to lower a ketone frequency. The band displacements must therefore be characteristic of the keto-enol ether grouping.

Similar differences in C=O frequency and intensity are shown by 2′- and 4′-enol ether analogues of griseofulvin, in which at least one of the 4-, 6-, or 2′-methoxyl groups has been replaced by ethoxyl, propoxyl, isopropoxyl, butoxyl, hexyloxyl, allyloxyl, phenoxyl, or benzyloxyl (see Table 1). In general, the 3- and the 4′-ketones of a 2′-enol ether absorb at 1708—1704 and 1656—1650 cm.$^{-1}$, respectively, and the 3- and 2′-ketones of a 4′-enol ether at 1698—1694 and 1664—1658 cm.$^{-1}$, respectively; the 3-ketone band of a 2′-enol ether (apparent ε 760—830) is more intense than the corresponding 4′-ketone band (apparent ε 500—710), whereas the 3-ketone band of a 4′-enol ether (apparent ε 530—640) is weaker than the corresponding 2′-ketone band (apparent ε 700—880). Similar carbonyl frequency and relative intensity changes are shown by epigriseofulvin[3] (Table 3). It is to be inferred that the changes (cf. Zbinden and Hall[8] and references there cited) are associated with strain on the spiro-carbon-2, and with resulting changes in bond angle there.

A 3′-alkyl substituent (see Table 4) raises by about 14 cm.$^{-1}$ the 4′-ketone frequency of griseofulvin, but lowers by about 6 cm.$^{-1}$ the 2′-ketone frequency of isogriseofulvin; the 3-ketone frequency is unchanged. Further, in the isogriseofulvin derivative, the intensity of the 3-ketone band (apparent ε $\sim$700) becomes slightly greater than that of the 2′-ketone (apparent ε $\sim$650); the intensity of the 3-ketone band for the griseofulvin derivative (apparent ε $\sim$780), however, remains considerably greater than that of the 4′-ketone (apparent ε $\sim$600). It is, therefore, still possible to distinguish between isomeric 2′- and 4′-enol ethers.

3′-Halogenation of griseofulvin and isogriseofulvin (see Tables 4 and 5) does not affect the 3-ketone frequency, but displaces the 4′- and 2′-ketone bands, respectively, to higher frequencies (cf. Cummins and Page[7] and references there cited). Chlorine, bromine, and iodine raise the 4′-ketone frequency of 2′-enol ethers by about 36, 30, and 20 cm.$^{-1}$, respectively, and that of the 2′-ketone of 4′-enol ethers by 18, 14, and 8 cm.$^{-1}$, respectively. 3′-Halogeno-4′-enol ethers frequently show a third, weak C=O band at about the same frequency, 1708—1704 cm.$^{-1}$, as that of the 3-ketone band for the corresponding 3′-halogeno-2′-enol ether. The relative intensities of the C=O bands for isomeric analogues are otherwise similar to those for griseofulvin and isogriseofulvin.

5-Alkylation and 5-halogenation of griseofulvin (see Table 5) has little effect on C=O frequency and intensity. If the 2′- and 4′-methoxyls of griseofulvin and isogriseofulvin, respectively, are replaced by chlorine (see Table 3), the isomeric products have approximately the same carbonyl frequencies. The isomers can, however, be distinguished by comparing band intensities. In the 2′-chloro-isomer, the 3-ketone band (1706 cm.$^{-1}$) is more intense than the 4′-ketone (1684 cm.$^{-1}$), whereas in the 4′-chloro-isomer the 3-ketone band is less intense than the 2′-ketone; similar intensity differences are shown by 3′-alkyl and 3′-halogen derivatives.

If either the 2′-methoxy-group of griseofulvin or the 4′-methoxy-group of isogriseofulvin is replaced by an alkylthio-group (see Table 6), the corresponding 4′- or 2′-ketone frequency is lowered slightly; the relative intensities of the 3- and 4′-ketone and 3- and 2′-ketone bands are unchanged. The 2′- and 4′-alkylthio-enol ethers can therefore be

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[6] Roberts, Gallagher, and Jones, " Infrared Absorption Spectra of Steroids. An Atlas," Vol. II, Interscience Publ., Inc., New York, 1958, p. 24.

[7] Cummins and Page, *J.*, 1957, 3847.

[8] Zbinden and Hall, *J. Amer. Chem. Soc.*, 1960, **82**, 1215.

TABLE 3.

Absorption bands (cm.$^{-1}$) for miscellaneous derivatives of griseofulvin and isogriseofulvin ($CHBr_3$ solution).

Compound			Ref.	C=O stretching	C=C stretching	1490—1210	1090—730
	R	R′					
III	H	—	*i*	1708s 1692s	1612s 1595s 1506s	1468—1462s 1436s 1416—1408s 1385w 1350s 1248m 1218s	1074m 1040s 998—990s 956w 935m 894s 862m 800s 790m
IV	H	—	*i*	1726s 1696s	1616s 1596s 1508s	1468—1464s 1438s 1415s 1385w 1350s 1265w 1245m 1220s	1068s 1042s 1002s 916m 880m 830w 800s 782m
III	MeO	—		1718s 1696s	1615—1598s 1508s	1470—1464s 1440s 1416—1412s 1380w 1350s 1262s 1220s	1052s 1024m 1000s 982m 966m 950m 890s 838w 800s 792m
IV	MeO	—	*j*	1726s 1692s	1615s 1592s 1508s	1470—1464s 1438s 1410s 1382m 1350s 1260m 1220s	1080s 1000s 970m 955m 902w 880m 828w 800s 782m
V	H	H	*i*	1708s 1695s 1675s	1615—1595s 1508s	1468—1462s 1438s 1416—1408s 1388m 1352s 1245s 1220s	1038s 998s 980s 938m 905m 886s 840w 800s 785w 750m
VI	H	H	*i*	1696s 1684s	1616—1594s 1506s	1468—1464s 1438s 1416—1408s 1390w 1384w 1350s 1240s 1220s	1060s 1000s 982m 954m 900w 882m 828s 796s 772w 730w
V	Cl	H	*f*	1706s 1684s	1614s 1592s 1506s	1468—1462s 1438s 1416—1406s 1385w 1350s 1242s 1220s	1078m 1052m 1000s 980m 955m 910w 892s 855m 838w 800s 782w 770w
VI	Cl	H	*f*	1705s 1684s	1614s 1590s 1506s	1468—1462s 1438s 1418s 1408s 1386w 1350s 1278m 1236s 1220s	1068s 1005s 975w 900w 890w 868s 836m 800s 770w
V	Cl	Pr^n	*f*	1706s 1680s	1614s 1592s 1508s	1468—1462s 1438s 1416—1408s 1386w 1350s 1246m 1220s	1080m 1040w 1000s 976m 952m 912w 902w 880m 838m 800s 776w
V	Cl	CH_2Ph	*f*	1706s 1680s	1614s 1590s 1508s 1498w	1468—1460s 1438s 1418—1408s 1386w 1352s 1246s 1220s	1076m 1030w 998s 978w 952m 900w 884m 840m 800s 774w
VI	Cl	CH_2Ph	*f*	1700s 1678s	1615s 1592s 1508s 1498w	1468—1462s 1438s 1422m 1408s 1384w 1350s 1245m 1220s	1020m 1000s 972w 958m 914w 886m 870w 826w 800s 785w
V	Cl	Cl	*f*	1708s 1700s	1614s 1590s 1506s	1468—1462s 1438s 1412—1406s 1385w 1350s 1260s 1246s 1220s	1060m 1000s 980m 962s 900w 890m 852w 806m 800s 764m 750m
VI	Cl	Cl	*f*	1708s 1692s	1614s 1590s 1506s	1468—1462s 1438s 1422s 1406s 1386w 1352s 1242s 1220s	1072s 1002s 982w 978w 910m 900w 860m 808m 798s 786s
V	Cl	Br	*f*	1708s 1698s	1612s 1590s 1506s	1468—1462s 1438s 1414—1406s 1385w 1350s 1244s 1220s	1054m 1000s 978m 956s 934w 890m 848w 800s 772m 742w
VI	Cl	Br	*f*	1706s 1690s	1612s 1586s 1506s	1468—1462s 1436s 1420s 1405s 1385w 1350s 1230—1220s	1078s 1062s 1000s 974w 890m 850m 802m 798s 774s 764w
Dechlorogriseofulvin			*k*	1720w 1692s 1650s	1620—1594s 1502s	1468—1460s 1434—1426s 1385m 1356s 1280w 1246s 1230—1218s	1058s 1046m 996s 968s 938w 912w 878w 860w 834m 820s 800w 780w
Dechloroisogriseofulvin			*k*	1725w 1690s 1656s	1620—1592s 1502s	1468—1456s 1445s 1428—1424s 1386s 1372s 1345s 1330s 1230—1216s	1068s 1042m 1016m 994s 938w 912w 882w 867w 830s 818s 800w 778w
Epigriseofulvin			*h*	1706s 1656s	1616s 1592s 1508s	1470—1462s 1438s 1406s 1386m 1352s 1276w 1250s 1228—1220s	1076s 1050s 1022w 986s 972s 948s 914m 896s 878m 838m 800s 770w

References: See Table 1; *i*, ref. 1*c*; *j*, ref. 1*b*; *k*, MacMillan, *J.*, 1953, 1697.

distinguished. Introduction of 3′-propyl or 3′-benzyl into 2′-alkylthio-analogues of griseofulvin (Table 7) does not affect the 3-ketone band, but displaces the 4′-ketone band further (22—26 cm.$^{-1}$) than was observed for the corresponding 2′-alkoxy-compound (10—14 cm.$^{-1}$).

C=C *Stretching Bands.*—The bands at about 1615 and 1508 cm.$^{-1}$ in the infrared spectra of griseofulvin are C=C skeletal in-plane vibrations of the aromatic ring-A and are present in the spectra of all griseofulvin derivatives listed in Tables 1—7 that have a 5-hydrogen atom. In many derivatives the 1615 cm.$^{-1}$ band broadens and extends to about 1595 cm.$^{-1}$; this range is given in the Tables. The 1508 cm.$^{-1}$ band is displaced to 1502 cm.$^{-1}$ in the spectra of dechloro-griseofulvin and -isogriseofulvin (Table 3) and to about 1472 cm.$^{-1}$ in 5-alkyl and 5-halogen derivatives (Table 5); these displacements provide a useful test for the substitution pattern of ring A.

The 2′-ethylenic linkage of griseofulvin absorbs sharply at 1591 cm.$^{-1}$; the corresponding 3′-ethylenic linkage for isogriseofulvin absorbs close to the strong aromatic-ring band at 1614—1598 cm.$^{-1}$ and cannot always be resolved from it. Similar displacements are shown by the 2′- and 3′-ethylenic linkages of alkoxy-analogues of griseofulvin and isogriseofulvin, respectively. The 1- and 2-ethylenic linkages of 1-methoxycholest-1-en-3-one and 3-methoxycholest-2-en-1-one, which are analogous to the 2′- and 3′-ethylenic linkages of griseofulvin and isogriseofulvin, absorb at 1588 and 1616 cm.$^{-1}$, respectively.

3′-Alkylation and 3′-halogenation (Table 4) have little effect on the 2′-ethylenic band of a 2′-enol ether, but 3′-chlorine, 3′-bromine, and 3′-iodine displace the 3′-ethylenic band of a 4′-enol ether to 1590—1588, 1588—1584, and 1578—1574 cm.$^{-1}$, respectively. The aromatic C=C bands at 1616—1600 and 1508 cm.$^{-1}$ are unchanged.

2′- and 4′-Phenoxy-analogues show additional aromatic C=C bands at 1592 and 1492—1490 cm.$^{-1}$. Benzyl, benzyloxy-, and benzylthio-groups absorb weakly, but distinctly, at 1500—1498 cm.$^{-1}$; the corresponding 1600 cm.$^{-1}$ bands are masked by aromatic ring-A bands.

The spectra of 2′- and 4′-alkylthio-analogues of griseofulvin (Table 6) reveal three discrete bands between 1616 and 1568 cm.$^{-1}$. The relatively weak, low-frequency, bands at 1570—1568 and 1572 cm.$^{-1}$ are assigned to the 2′- and 3′-ethylenic linkages of the 2′- and 4′-alkylthio-analogues, respectively. This displacement of the 2′- and 3′-ethylenic bands is largely eliminated by the introduction of a 3′-propyl or 3′-benzyl group, but is increased by 3′-halogen (see Table 7). The ring-A aromatic C=C bands at about 1614, 1590, and 1508 cm.$^{-1}$ are unaffected by these substitutions.

The great intensity of the C=C bands (apparent ε 1600—2500), compared with that of the C=O bands (apparent ε, about 500—800), is a notable feature of the spectra of griseofulvin and its analogues;[1a] their strength is relatively unaffected by substitutions in rings A and C and is only reduced when a ring is opened. Most of the increased intensity can be associated with the aromatic C=C bands; the 1590 cm.$^{-1}$ band for griseofulvin (apparent ε ~800), which is probably associated with the 2′-ethylenic linkage, is nevertheless slightly stronger than the corresponding 4′-ketone band (apparent ε ~500). Similarly, the C=C bands for 1-methoxycholest-1-en-3-one and 3-methoxycholest-2-en-1-one are slightly stronger than the corresponding ketone bands.

Erskine and Waight[9] have shown that, whereas in rigidly *transoid* $\alpha\beta$-unsaturated ketone systems the C=O band is much stronger than the C=C stretching band, in *cisoid* systems the C=O and C=C bands are of more nearly equal intensity. This observation will not explain the strength of the C=C bands of the two steroids and of griseofulvin and its analogues; in these compounds the $\alpha\beta$-unsaturated ketone system is *transoid*. The abnormal C=C band intensities must, therefore, like the unusual C=O band displacements discussed above, be a special feature of the keto–enol ether system. The same explanation may account for the intense aromatic C=C bands; ring A could be visualised as part of a keto–enol ether system.

[9] Erskine and Waight, *J.*, 1960, 3425.

TABLE 4.

Absorption bands (cm.$^{-1}$) for 3′-alkyl and 3′-halogen derivatives (CHBr$_3$ solution).

Compound			Ref.	C=O stretching	C=C stretching	1490—1210	1090—730
	R	R′					
V	MeO	Me	*e*	1704s 1668s	1616—1594s 1508s	1468—1462s 1436s 1414—1408s 1384m 1350s 1250s 1220s	1022m 1002m 986s 970s 890m 880m 828m 798s 770w
VI	MeO	Me	*e*	1696s 1656s	1616—1594s 1508s	1468—1464s 1440s 1422m 1410s 1390s 1350s 1248s 1220s	1025m 1006s 988m 962s 928m 880m 826s 802s 798s 778w
V	MeO	CH$_2$Ph	*e*	1706s 1665s	1615—1592s 1508s 1498m	1468—1462s 1438s 1414—1408s 1385m 1350s 1250s 1220s	1060s 1034w 1002s 976m 964m 896w 872m 800s 775w
VI	MeO	CH$_2$Ph	*e*	1696s 1656s	1615—1595s 1508s 1498m	1470—1462s 1438s 1418—1408s 1380s 1350s 1250s 1220s	1085m 1030w 1020m 1004s 987m 967m 922m 896w 873m 820w 800s 775w
V	EtO	Et	*e*	1706s 1666s	1616s 1592s 1508s	1468—1462s 1438s 1414—1408s 1388m 1370m 1350s 1250s 1220s	1040s 1020m 1000s 975m 944w 910w 898w 856w 836m 800s 780w 762w
VI	EtO	Et	*e*	1694s 1652s	1616—1592s 1508s	1470—1462s 1438s 1424w 1410s 1388s 1350s 1252s 1220s	1048m 1022s 1008s 980w 962w 938m 912m 872m 836s 810m 800s 782w
V	MeO	Cl	*l*	1706s 1690s	1615—1592s 1508s	1468—1462s 1438s 1414—1406s 1385w 1350s 1274—1260s 1220s	1054s 1000s 966m 950m 914w 890m 818s 800s 778m
VI	MeO	Cl	*l*	1706m 1692s 1678s	1614—1590s 1508s	1468—1460s 1438s 1418—1410s 1385w 1370s 1345s 1260s 1220s	1060s 1000s 980w 940m 900w 890m 812s 794s
V	MeO	Br	*l*	1706s 1686s	1615—1592s 1508s	1470—1462s 1438s 1412—1408s 1386w 1354w 1268—1254s 1220s	1050s 1000s 980m 960s 908w 890s 805s 800s 776m 762w
VI	MeO	Br	*l*	1706m 1696s 1674s	1616s 1586s 1508s	1470—1462s 1438s 1418—1410s 1386w 1370s 1354s 1350s 1258s 1220s	1056s 1002s 980w 938m 888m 806m 798s 782s
V	MeO	I	*l*	1704s 1674s	1615s 1590s 1508s	1470—1462s 1438s 1412—1408s 1386w 1350s 1250s 1220s	1046s 1000s 975m 956m 890s 800s 775w 756w
VI	MeO	I	*l*	1694s 1668s	1616s 1578s 1508s	1470—1462s 1438s 1414—1408s 1385w 1350s 1256s 1220s	1050s 1000s 936m 882m 798s

The following analogues (ref. *e*) were also measured: (V; R = MeO, R′ = Pr^n or CH$_2$:CH·CH$_2$); (VI; R = MeO, R′ = Pr^n or CH$_2$:CH·CH$_2$); (V; R = EtO, R′ = CH$_2$Ph); (VI; R = EtO, R′ = CH$_2$Ph), (V; R = Pr^{n}O, R′ = Pr^n or CH$_2$Ph), (VI; R = Pr^{n}O, R′ = Pr^n or CH$_2$Ph), (V; R = Bu^{n}O, R′ = CH$_2$Ph) and (VI; R = Bu^{n}O, R′ = CH$_2$Ph); (ref. *l*) (V; R = EtO, R′ = Cl, Br, or I); (VI; R = EtO, R′ = Cl, Br, or I); (V; R = Pr^{n}O, R′ = Cl, Br, or I); (VI; R = Pr^{n}O, R′ = Cl, Br, or I); (V; R = Bu^{n}O, R′ = Cl, Br, or I); and (VI; R = Bu^{n}O, R′ = Cl, Br, or I).

For references see earlier Tables; *l*, ref. 2*c*.

TABLE 5.

Absorption bands (cm.$^{-1}$) for 5-alkyl and 5-halogen derivatives (CHBr$_3$ solution).

Compound			Ref.	C=O stretching	C=C stretching	1490—1210	1090—730
	R	R′					
VII	Pr^n	H	*d*	1710s 1658s	1610s 1580s	1474s 1464s 1430s 1418m 1398s 1358s 1344m 1280w 1252s 1230s	1060s 1022m 990m 975m 960s 922m 892w 870w 848m 836s 796w 780w 748w
VII	Allyl	H	*d*	1710s 1656s	1608s 1580s	1474s 1460s 1435s 1418m 1398s 1358s 1342m 1282w 1252s 1230s	1060s 1028m 990m 975w 960s 922m 880w 850m 838s 795w 780w 754w
VII	Cl	H	*l*	1712s 1655s	1612s 1570s	1470s 1460s 1440w 1418s 1385s 1352—1340s 1280s 1234—1228s	1088s 1060—1056s 1014m 980—970s 952s 915w 888w 838m 815s 786w 760s
VIII	Cl	H	*l*	1704s 1658s	1605s 1572s	1470s 1460s 1445m 1420s 1388s 1350m 1332m 1280m 1232—1226s	1088s 1020—1014m 995s 980m 955s 912w 882m 840s 812m 788w 762s
VII	Cl	Cl	*l*	1712s 1688s	1600s 1570s	1472s 1460s 1418s 1388s 1350m 1278s 1260m 1236s	1055s 1016m 978m 962s 948s 914m 892w 823s 802w 774w 758m
VIII	Cl	Cl	*l*	1704s 1674s	1596—1580s 1570s	1472s 1458s 1418s 1386s 1370s 1352w 1278m 1260s 1240s 1223s	1062s 1022m 1002m 980m 958s 940s 900w 888w 820s 802m 790m 745m
VII	Br	H	*l*	1712s 1656s	1614s 1600s 1568s	1472—1460s 1445w 1416s 1385s 1356—1348s 1280s 1232s	1088s 1058s 1012s 978m 970s 952s 916w 885m 836m 806s 782w
VIII	Br	Br	*l*	1712s 1682s	1594s 1562s	1472—1460s 1414s 1380s 1348m 1280s 1260s 1245s 1230s	1048s 1010m 975m 962s 946s 902m 882m 810s 782w 762m

Carbon–Hydrogen Deformation Bands.—The various alkoxyl and alkyl groups of griseofulvin and its analogues show a series of C–H deformation bands in the 1480—1350 cm.$^{-1}$ region. We have, in accordance with Katritzky and Coats's assignments for simple methoxybenzenes [10] (see also ref. 11), attributed the 1470—1462 and 1438 cm.$^{-1}$ bands of griseofulvin and isogriseofulvin to asymmetrical and symmetrical CH_3 bending, respectively. These bands have the same frequencies and relative intensities in all griseofulvin derivatives as have 4-, 6-, and either 2′- or 4′-methoxy-groups.

The 1416—1408 cm.$^{-1}$ bands include vibrations associated with the 5′-methylene group and, possibly, with aromatic ring A; they are probably present, although sometimes masked by stronger bands, in the spectra of all griseofulvin derivatives. The weak band at 1388—1384 cm.$^{-1}$ in the spectra of griseofulvin and other 2′-enol ethers, which is, however, masked in the spectra of isogriseofulvin and 4′-enol ethers, is the C–H symmetrical bending band for the 6′-methyl group; the corresponding asymmetrical band probably contributes to the 1470—1462 cm.$^{-1}$ band.

Replacement of the methoxy-groups of griseofulvin by one, two, or three ethoxy-groups progressively weakens the 1470—1462 and 1438 cm.$^{-1}$ bands and leads to the appearance of strong ethoxy-bands at about 1416 and 1380 cm.$^{-1}$. We (cf. Katritzky and Coats [10]) have assigned the 1474 and 1386—1378 cm.$^{-1}$ bands of the triethoxy-analogues of griseofulvin and isogriseofulvin to CH_2 scissoring and wagging vibrations, respectively, and the 1446 and 1416 cm.$^{-1}$ bands to asymmetrical and symmetrical CH_3 bending vibrations, respectively; the remaining bands at 1460 and 1398 cm.$^{-1}$ may include aromatic-ring vibrations. Introduction into ring C of larger alkoxy-groups, such as butoxy and allyloxy, causes similar progressive spectral changes.

2′-Demethoxygriseofulvin (V; R = R′ = H), 4′-demethoxyisogriseofulvin (VI; R = R′ = H), 2′-dihydrogriseofulvin (III; R = MeO), 3′-dihydroisogriseofulvin (IV; R = MeO) (see Table 3), and 3′-alkyl and 3′-halogen derivatives of griseofulvin (see Table 4) show the additional C–H deformation bands that might be expected from their structures. Isomeric 2′- and 4′-alkylthio-analogues do not exhibit big spectral differences in this region.

Carbon–Oxygen Stretching Bands.—Griseofulvin and its alkoxy-analogues show strong bands at about 1350, 1225, 1140, and 1100 cm.$^{-1}$. The first two bands are probably C–O–C asymmetric stretching bands and the last two, which are obscured by solvent absorption in bromoform solution spectra but may be observed at 1140—1132 and 1105—1096 cm.$^{-1}$, respectively, in chloroform solution or Nujol mull spectra, are probably skeletal vibrations. The 1350 cm.$^{-1}$ band has a higher frequency than those (1330—1273 and 1288—1225 cm.$^{-1}$) assigned to C–O–C asymmetric stretching of simple methoxybenzenes by Katritzky and Coats.[10]

Griseofulvin and 2′-enol ethers differ characteristically from isogriseofulvin and 4′-enol ethers in this region; griseofulvin and 2′-enol ethers absorb about 30% more strongly at 1350 and 1225 cm.$^{-1}$, whereas isogriseofulvin and 4′-enol ethers absorb 2—4 times as strongly at 1388 and 1175 cm.$^{-1}$. 2′-Enol ethers, but not 4′-enol ethers, have a weak band at 1282—1280 cm.$^{-1}$. Similar differences are shown by carbon disulphide solution spectra of 1-methoxycholest-1-en-3-one and 3-methoxycholest-2-en-1-one; the former absorbs more strongly at 1346, 1276, and 1225 and the latter at 1380 and 1176 cm.$^{-1}$. The 1388 and 1175 cm.$^{-1}$ bands for isogriseofulvin and 4′-enol ethers must therefore be associated with ring-oxygen stretching of the 4′-alkoxy-group; the 4- and 6-alkoxyl groups absorb at 1350 and 1225 cm.$^{-1}$, and the ring-oxygen stretching bands for the 2′-, 4-, and 6-alkoxyl groups of griseofulvin and of 2′-enol ethers also have these frequency values.

3′-Alkylation and 3′-halogenation of griseofulvin and isogriseofulvin do not affect the 1350 cm.$^{-1}$ band, but weaken the 1225 cm.$^{-1}$ band (Table 4); additional bands for the 3′-alkyl, 3′-chlorine, 3′-bromine, and 3′-iodine derivatives appear at 1250—1246, 1274—1260, 1268—1252, and 1256—1248 cm.$^{-1}$, respectively. 5-Alkylation (Table 5) weakens

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[10] Katritzky and Coats, *J.*, 1959, 2062.

[11] Briggs, Colebrook, Fales, and Wildman, *Analyt. Chem.*, 1957, **29**, 904.

TABLE 6.

Absorption bands (cm.$^{-1}$) for 2′-alkylthio-analogues of griseofulvin and 4′-alkylthio-analogues of isogriseofulvin (CHBr$_3$ solution).

Compound [2d]			C=O stretching	C=C stretching	1490—1210	1090—730
	R	R′				
V	MeS	H	1706s 1648s	1614s 1590s 1570s 1508s	1470—1462s 1438s 1414—1408s 1386m 1350s 1270m 1245s 1220s	1046m 1000s 978m 954m 910w 886s 850w 840w 800s 778w 770w
VI	MeS	H	1695s 1654s	1614s 1590s 1572s 1508s	1470—1462s 1438s 1420s 1408s 1384w 1350s 1244s 1220s	1068s 1004s 974w 955w 900w 882m 858s 840m 880s 786w 772w
V	EtS	H	1704s 1648s	1614s 1590s 1570s 1508s	1470—1462s 1438s 1414—1408s 1386w 1350s 1260m 1245s 1220s	1050m 1000s 978m 954s 912w 888s 870w 852— 842w 800s 780w
VI	EtS	H	1694s 1656s	1614s 1590s 1572s 1508s	1470—1462s 1438s 1420s 1410s 1385w 1350s 1244s 1220s	1068s 1008s 978m 918w 905w 886w 860s 842m 800s 874w
V	Pr^{n}S	H	1706s 1648s	1615s 1592s 1568s 1508s	1470—1462s 1438s 1416—1408s 1386m 1352s 1270m 1246s 1220s	1048m 1000s 980m 956m 912w 888s 840w 800s 780w 770w
V	Bu^{n}S	H	1705s 1648s	1615s 1592s 1568s 1508s	1468—1460s 1438s 1414—1406s 1386m 1350s 1270m 1244s 1220s	1048m 1000s 978m 954m 910w 886s 840w 800s 780w 772w
V	CH$_2$:CH·CH$_2$·S	H	1705s 1648s	1615s 1590s 1568s 1508s	1470—1462s 1438s 1414—1408s 1388m 1350s 1270m 1246s 1220s	1048m 1000s 980m 954m 930m 888—870s 840w 800s 780w 770w
VI	PhS	H	1696s 1658s	1616s 1588— 1580s 1508s	1470—1462s 1438s 1420s 1408s 1386w 1352s 1285m 1246s 1220s	1068s 1030w 1008s 976w 918w 906w 888w 866m 840m 800s 776w 752s
V	Ph·CH$_2$·S	H	1704s 1648s	1614s 1590s 1568s 1508s 1500m	1468—1460s 1438s 1414—1406s 1386w 1350s 1270m 1242s 1220s	1047m 1030w 1000s 978w 954m 912w 886s 838w 800s 780w
VI	Ph·CH$_2$·S	H	1694s 1656s	1614s 1590s 1574s 1508s 1500m	1470—1462s 1438s 1420s 1408s 1384w 1350s 1260m 1240s 1220s	1068s 1030w 1004s 970w 917w 902w 884w 856m 840m 800s 786w 770w

TABLE 7.

Absorption bands for 3′-alkyl and 3′-halogen derivatives of 2′-alkylthio-analogues (CHBr$_3$ solution).

Compound [2d]			C=O stretching	C=C stretching	1490—1210	1090—730
	R	R′				
V	MeS	Pr^n	1704s 1672s	1614s 1590s 1508s	1468—1462s 1438s 1414—1408s 1385w 1352s 1245m 1220s	1080m 1040w 996s 975m 950m 910w 900w 890—878m 835w 800s 776w
V	MeS	CH$_2$Ph	1704s 1674s	1616s 1592s 1508s 1498m	1470—1462s 1438s 1415—1410s 1386w 1352s 1245m 1220s	1074m 1034w 998s 978m 955m 904w 882m 838w 798s 776w
V	MeS	Cl	1708s 1692s	1614s 1592s 1550m 1508s	1468—1462s 1438s 1414—1406s 1386w 1350s 1254—1246s 1220s	1054m 996s 978m 956s 888m 800s 775w 748w
V	MeS	Br	1706s 1692s	1614s 1592s 1548m 1508s	1468—1460s 1438s 1414—1408s 1386w 1350s 1242s 1220s	1050m 998s 978m 952m 930w 888m 800s 772w

The following analogues (ref. 2*d*) were also examined: (V; R = Pr^{n}S, Bu^{n}S, CH$_2$:CH·CH$_2$·S, or Ph·CH$_2$·S, R′ = Pr^n); (V; R = EtS, Pr^{n}S, Bu^{n}S, CH$_2$:CH·CH$_2$·S, or Ph·CH$_2$·S, R′ = Ph·CH$_2$); and (V; R = EtS, Pr^{n}S, Bu^{n}S, CH$_2$:CH·CH$_2$·S, or Ph·CH$_2$·S, R′ = Cl).

the 1350 cm.$^{-1}$ band and displaces the 1225 cm.$^{-1}$ band to about 1252 cm.$^{-1}$. 5-Halogenation moves the 1350 cm.$^{-1}$ band to about 1388—1380 cm.$^{-1}$ and displaces the 1225 cm.$^{-1}$ band slightly.

Replacement of the 2′-methoxyl of griseofulvin and the 4′-methoxyl of isogriseofulvin by an alkylthio-group (Table 6) leads, as might be expected, to a weakening of the 1350 and 1225 cm.$^{-1}$ bands, and it becomes less easy to distinguish in this spectral region between the two isomers; a new band of medium intensity, probably an alkylthio C–H deformation band, appears at 1246—1240 cm.$^{-1}$.

We were unable to identify between 1300 and 900 cm.$^{-1}$ the pattern of alkylthio C–H deformation and skeletal bands reported by Boonstra and Rinzema.[12] The alkylthio-bands are probably weaker than, and are masked by, the relatively strong C–O stretching bands. The conjugation effects in our compounds would also cause a displacement of the bands (see below).

The C–O symmetrical stretching bands for griseofulvin and its 2′-methoxy-analogues and for isogriseofulvin and its 4′-methoxy-analogues at 968—960 and 1010—995 cm.$^{-1}$, respectively, like those for 1-methoxycholest-1-en-3-one and 3-methoxycholest-2-en-1-one at 980 and 996 cm.$^{-1}$, respectively, but unlike those for simple methoxy- and ethoxybenzenes at 1048—1013 and 1050—1034 cm.$^{-1}$, respectively,[10] are much weaker than the corresponding asymmetrical bands. The bands are displaced by 3′-alkyl and 3′-halogen substituents and by new 2′- and 4′-alkoxy-substituents. The corresponding bands for 2′- and 4′-ethoxyl, 2′- and 4′-propoxyl, 2′- and 4′-isopropoxyl, 2′- and 4′-butoxyl, and 2′- and 4′-allyloxyl are 1052—1048 and 1028—1020, 1058 and 1058, 1034 and 1062, 1045—1040 and 1065—1060, and 1042 and 1066 cm.$^{-1}$, respectively.

All griseofulvin and isogriseofulvin derivatives, except 5-alkyl and 5-halogen derivatives, with the same relative configuration at position 2 as griseofulvin, (2*S*,6′*R*)-7-chloro-4,6,2′-trimethoxy-6′-methylgris-2′-en-3,4′-dione, show a strong band at 1000 cm.$^{-1}$, which shifts to about 948 cm.$^{-1}$ in the spectrum of the 2*R*,6′*R*-diastereoepimer, epigriseofulvin.[3] These bands, which probably represent a stretching vibration of the $O_{(1)}$–$C_{(2)}$ linkage, provide a method for distinguishing between the two epimers. 5-Alkyl and 5-halogen derivatives of griseofulvin (Table 5) are readily distinguished from the epimeric form; whereas epigriseofulvin absorbs normally at 1508 cm.$^{-1}$, the 5-alkyl and 5-halogen derivatives show a displaced aromatic C=C band at about 1472 cm.$^{-1}$.

The 960—400 cm.$^{-1}$ *Region.*—Griseofulvin and isogriseofulvin show 2′- and 3′-double-bond C–H bending bands at 838 and 842 cm.$^{-1}$, respectively. Similar bands appear at 838—832 and 844—842 cm.$^{-1}$, respectively, in the spectra of all 2′- and 4′-enol ethers with a 3′-hydrogen atom; 2′-dihydrogriseofulvin (III; R = MeO), 3′-dihydroisogriseofulvin (IV; R = MeO), and 3′-alkyl and 3′-halogen derivatives do not give the band. The bands are weaker in the spectra of alkylthio-analogues and are displaced in the spectra of 2′- and 4′-chloro-compounds. 1-Methoxycholest-1-en-3-one and 3-methoxycholest-2-en-1-one show double-bond C–H bending bands at 822 and 830 cm.$^{-1}$, respectively.

All griseofulvin analogues with a 5-hydrogen atom absorb strongly at 800—796 cm.$^{-1}$. The position of the band is affected by changes in the substitution pattern of ring A (see Table 5). Introduction of 4,6-diethoxy-groups depresses the band position to 790 cm.$^{-1}$, whereas removal of the 7-chlorine atom raises the band to 820—818 cm.$^{-1}$. The 800—796 cm.$^{-1}$ band is possibly a C–H out-of-plane deformation band for the aromatic ring. The 890—882 cm.$^{-1}$ band, which appears in the spectra of most 7-chloro-analogues of griseofulvin, disappears on dechlorination; substitution at position 5 splits the band into a weak doublet at 885—868 cm.$^{-1}$.

Griseofulvin and isogriseofulvin do not absorb strongly between 960 and 900 cm.$^{-1}$, but their 4-, 6-, 2′-, and 4′-ethoxy-analogues show medium-intensity C–C stretching

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[12] Boonstra and Rinzema, *Rec. Trav. chim.*, 1960, **79**, 962; see also Menefee, Alford, and Scott, *J. Org. Chem.*, 1957, **22**, 792; Scott and McCullough, *J. Amer. Chem. Soc.*, 1958, **80**, 3554.

ethyl bands at 940—914 cm.$^{-1}$ (cf. Katritzky and Coats[10]). Allyloxy- and allylthio-derivatives yield medium-intensity CH_2 out-of-plane deformation bands at 938—932 and 930—926 cm.$^{-1}$, respectively; a weak overtone band at about 1850 cm.$^{-1}$ was usually detected, but the corresponding C–H out-of-plane deformation band, at about 990 cm.$^{-1}$, was not readily distinguished from other bands in the 1000 cm.$^{-1}$ region (cf. ref. 13).

Phenoxy- and benzyloxy-analogues of griseofulvin and isogriseofulvin absorb relatively strongly at 778—772 and 736—730 cm.$^{-1}$, respectively; Nujol mull or carbon disulphide solution spectra show additional phenoxy- and benzyloxy-bands at 685—682 and 695—688 cm.$^{-1}$, respectively. Benzylthio- and 3′-benzyl derivatives, as Nujol mulls, absorb at about 725 and 700 cm.$^{-1}$.

Nujol mull spectra of our alkylthio-compounds did not reveal any distinctive C–S stretching bands[12] in the 750—650 cm.$^{-1}$ region. Nevertheless, the bromoform solution spectra of the 2′-alkylthio-analogues showed strong bands at 956—954 and 888—886 cm.$^{-1}$, which were absent from, or much weaker in, the spectra of the corresponding 4′-alkylthio-isomers; the latter showed bands at 860—858 and 842—840 cm.$^{-1}$, which were not given by 2′-alkylthio-analogues. These bands were displaced and were much weaker in the spectra of 3′-alkyl and 3′-halogen derivatives.

A careful inspection of the 700—400 cm.$^{-1}$ region of the spectra of griseofulvin and its simple analogues did not yield much useful information. The spectra of isomeric 2′- and 4′-enol ethers differed considerably. The absorption bands appeared to be highly specific for each compound, and we were unable to provide a simple interpretation.

Experimental.—The griseofulvin analogues were examined over the 4000—650 cm.$^{-1}$ spectral region as 1·0% (w/v) and frequently as 0·1% (w/v) solutions in bromoform, stabilised with 0·05% of diphenylamine, in 0·8 mm. cells and as Nujol mulls by means of a Perkin–Elmer Corporation, model 21, double-beam infrared spectrophotometer fitted with a sodium chloride prism. Selected compounds were examined over the 1000—400 cm.$^{-1}$ region as saturated solutions in acetonitrile in 0·5 mm. cells, and as Nujol mulls in the same spectrophotometer fitted with a potassium bromide prism. The accuracy of frequency measurements for sharp bands was about ±3 cm.$^{-1}$ at 1700 cm.$^{-1}$ and ±2 cm.$^{-1}$ at 800 cm.$^{-1}$; the spectral slit width was about 6 cm.$^{-1}$ at 1700 cm.$^{-1}$.

The apparent molecular extinction coefficients were measured in triplicate on 0·1% (w/v) bromoform solutions and were calculated from the relation, $\varepsilon = (1/cl) \log_{10} (T_0/T)$, where T_0 and T are, respectively, the radiation (%) transmitted by the solvent and by the solution at the frequency of the absorption band, c is the solute concentration in moles per l., and l is the cell thickness in cm.

The effect of different solvents on the carbonyl and C=C frequency of griseofulvin and isogriseofulvin was determined by measuring the spectra of 0·5% (w/v) solutions in the solvents listed in Table 2 in 0·1 mm. cells at 2000—1500 cm.$^{-1}$. Replicate measurements were undertaken, and special care was taken to locate band positions with an error of less than ±2 cm.$^{-1}$.

All the compounds, with the exception of the two steroids and epigriseofulvin, were prepared in these laboratories and had the physical properties described in the references listed in the Tables.

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[13] Davison and Bates, *J.*, 1953, 2607; Tarbell and McCall, *J. Amer. Chem. Soc.*, 1952, **74**, 48.