# 339. *Griseofulvin Analogues. Part VIII.* Infrared Absorption of Griseofulvic Acid and Related Compounds.*

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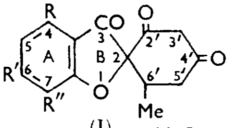
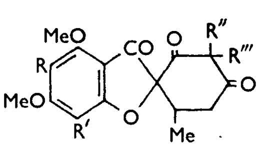
The infrared absorptions of 47 analogues of griseofulvic and dechloro-griseofulvic acid and of their 2′,4′-bisethylene ketals and of 22 analogues of griseofulvin and isogriseofulvin are described. The effects of carbonyl, alkyl, alkoxy-, alkylthio-, halogen, and basic substituents are discussed.

We have discussed previously[1] the infrared absorption spectra of simple analogues of griseofulvin and isogriseofulvin and have suggested structural assignments for their principal absorption bands. Our survey has now been extended to solid-state and solution spectra of griseofulvic acid (I; R = R′ = MeO, R″ = Cl) and of 46 related compounds. The solid state (Nujol mull or potassium chloride disc) spectra of griseofulvic acid and its simple analogues differ considerably from those of the corresponding bromoform solutions and are also frequently more complex than those for related griseofulvin and isogriseofulvin analogues. The differences are in general attributed to intermolecular hydrogen-bonding effects.



(I)



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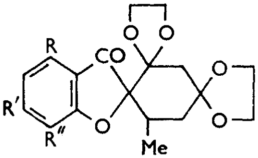

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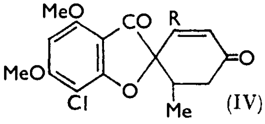
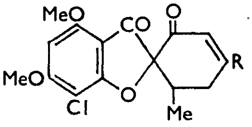


(IV)



(V)

*Carbonyl Stretching Bands.*—Griseofulvic acid and its simpler 4,6-dialkoxyl analogues, which are much less soluble in bromoform and in the normal infrared solvents than are griseofulvin and its analogues, were examined as saturated solutions in bromoform on an infrared spectrophotometer fitted with ordinate scale expansion (see Table 1). The solution spectra show a relatively weak carbonyl stretching band at 1744—1710 cm.$^{-1}$ and a more intense carbonyl band at 1694—1690 cm.$^{-1}$; additional absorption appears at 1676—1660 cm.$^{-1}$. The 3-ketone probably absorbs at 1694—1690 cm.$^{-1}$, and either the 2′- or 4′-ketone at 1676—1660 cm.$^{-1}$ as a result of conjugate chelation with the enolised 4′- or 2′-ketone, respectively.[2] The weak 1744—1740 cm.$^{-1}$ band, which is more prominent in dilute solution spectra, is probably caused by direct interaction between the 3-ketone and unenolised 2′-ketone and may have an origin similar to that of the displaced carbonyl stretching bands shown by 21-acetoxy-20-oxo-steroids.[3]

3′-Alkylation of griseofulvic acid (*e.g.*, II; R = R‴ = H, R′ = Cl, R″ = Me) leads to increased solubility in bromoform and displaces the carbonyl bands to 1718—1698 and 1668—1655 cm.$^{-1}$ (see Table 2); the former band is associated with the 3-ketone, which cannot enolise, and the latter band with an αβ-unsaturated ketone in enolised ring C. A weak band for bonded hydroxyl appears at 3450—3280 cm.$^{-1}$. 3′-Halogenation of griseofulvic acid affects the carbonyl frequency of the αβ-unsaturated ketone, but does

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* Part VII, *J.*, 1963, 1610.

[1] Page and Staniforth, *J.*, 1962, 1292.

[2] Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen & Co., Ltd., London, 1958, 2nd edn., p. 142.

[3] Jones, Humphries, and Dobriner, *J. Amer. Chem. Soc.*, 1950, **72**, 956.

TABLE 1.

Absorption bands (cm.$^{-1}$) for 4- and 6-alkoxy-analogues of griseofulvic acid and of dechlorogriseofulvic acid ($CHBr_3$ solution).

| Compound (I) | | | | | Absorption bands (cm.$^{-1}$) | | | |
|---|---|---|---|---|---|---|---|---|
| No. | R | R′ | R″ | Ref. | C=O stretching | C=C stretching | 1490—1210 | 1090—730 |
| 1 | HO | MeO | H | a | 1735w 1695m 1676s 1644s | 1610s 1600s | * | * |
| 2 | MeO | MeO | H | a | 1742m 1690s 1660s | 1616s 1592s 1502m | 1466—1460s 1435s 1384w 1368m 1350s 1242s 1220s | 1068m 1000s 968w 842m 820m |
| 3 | HO | MeO | Cl | b | 1745m 1685s 1665s | 1640s 1615s | * | * |
| 4 | MeO | HO | Cl | c | 1722m 1664s | 1640s 1612s 1590s 1538s | 1466s 1450s 1422—1410s 1390—1382m 1358s 1240s 1218m | 1070m 1008m 972w 920w 845m 814m |
| 5 | MeO | MeO | Cl | c | 1740m 1688s | 1610s 1592s 1506m | 1466—1460s 1434m 1402s 1386w 1348s 1285m 1216s | * |
| 6 | MeO | EtO | Cl | d | 1744m 1692s | 1614—1594s 1508m | * | * |
| 7 | MeO | Pr$^n$O | Cl | b | 1744m 1692s | 1614s 1590s 1508m | 1466—1460s 1448s 1410s 1384m 1356s 1248s 1216s | 1006m 978w 954w 920w 888w 850w 800m 766w |
| 8 | MeO | Pr$^i$O | Cl | b | 1744m 1692s | 1614s 1590s 1508m | 1466s 1448s 1420—1408s 1382m 1370m 1350m 1250m 1216s | 1000m 916w 888w 834w 800m |
| 9 | MeO | Bu$^n$O | Cl | b | 1744m 1692s | 1616s 1590s 1508m | 1466—1460s 1448s 1410s 1384m 1350s 1250s 1218s | 1006m 954w 920w 894w 844w 800m 780w |
| 10 | MeO | $C_{16}H_{33}O$ | Cl | b | 1745m 1692s | 1622—1590s 1508m | 1466s 1448s 1410s 1382m 1350s 1248m 1214s | 1006m 918w 888w 848w 800m 780w |
| 11 | MeO | $CH_2\colon CH\cdot CH_2O$ | Cl | b | 1744m 1690s | 1616s 1590s 1508m | 1468s 1448s 1412s 1384m 1350s 1252s 1218s | 1008m 980w 935w 890w 850w 800m 782w |
| 12 | MeO | $PhCH_2\cdot O$ | Cl | b | 1742m 1690s | 1616—1590s 1506s | 1466s 1444s 1408s 1384m 1350s 1340s 1250m 1218s | 1030w 1002s 978m 912w 890w 845w 798m 780w 738m |
| 13 | MeO | Pyrrolidin-1-yl | Cl | e | 1745m 1716m 1676s | 1612s 1572s 1520m | 1485m 1468—1454s 1424s 1388m 1362—1350s 1260s 1240s | 1068m 1006m 915w 868w 828w 798m |
| 14 | EtO | EtO | Cl | d | 1744m 1692s | 1616s 1596s | * | * |
| 15 | MeS | MeS | Cl | e | 1742m 1690s 1648s | 1616—1600s 1580s 1545s 1508m | 1454s 1430—1420s 1375m 1252m 1230s | 1055m 1010w 976m 962w 850m 810m |

* Insufficiently soluble to give measurable bands.

Refs.: (a) Ref. 4. (b) Arkley, Attenburrow, Gregory, and Walker, *J.*, 1962, 1260. (c) Grove, MacMillan, Mulholland, and Rogers, *J.*, 1952, 3949. (d) MacMillan, *J.*, 1959, 1823. (e) Gregory, Goodall, and Walker, preceding paper.

TABLE 2.

Absorption bands for 3′-substituted derivatives of griseofulvic and of dechlorogriseofulvic acid ($CHBr_3$ solution).

| Compound (II; R = H) | | | | | Absorption bands (cm.$^{-1}$) | | | |
|---|---|---|---|---|---|---|---|---|
| No. | R′ | R″ | R‴ | Ref. | C=O stretching | C=C stretching | 1490—1210 | 1090—730 |
| 16 | Cl | Me | H | f | 1698s | 1616s 1594s 1508m | 1468—1460s 1436s 1406s 1390m 1348s 1244m 1218s | 1002s 970m 918m 885w 832w 792m |
| 17 | Cl | Et | H | f | 1735w 1698—1690s | 1612—1590s 1506m | 1466s 1435m 1402s 1384m 1348s 1244m 1218s | 1012s 998s 960m 890m 832m 790m |
| 18 | Cl | Pr$^n$ | H | f | 1714m 1698s 1658m | 1616s 1594s 1508m | 1470—1462s 1438m 1408s 1388m 1352s 1234s 1220s | 1076m 1006s 918m 898w 868m 798m |
| 19 | Cl | $CH_2Ph$ | H | f | 1714m 1698s 1656s | 1616s 1594s 1508m 1500m | 1470—1462s 1438s 1408s 1386m 1350s 1246m 1220s | 1048w 1035w 1006m 975w 955w 924w 900w 878w 800m 776w |
| 20 | Cl | $CH_2{\cdot}CH_2Ac$ | H | f | 1710m 1694s 1655m | 1616—1570s 1508m | 1470—1462s 1438s 1410s 1384w 1348s 1248s 1218s | 1042w 1028w 1000s 978w 918w 880w 840w 818w 795s 875w |
| 21 | Cl | Me | Me | f | 1734m 1702—1690s | 1616s 1590s 1508m | 1470—1462s 1438s 1408s 1386m 1350s 1268w 1245m 1220s | 1062w 1032m 1000m 970m 892w 860m 800s 775w |
| 22 | Cl | $CH_2Ph$ | $CH_2Ph$ | f | 1732m 1692s | 1616s 1592s 1508s 1500m | 1470—1462s 1438s 1408s 1386w 1350s 1244m 1220s | 1066m 1032w 1000s 964w 944w 918w 860m 798s 774w 752m |
| 23 | Cl | $NO_2$ | H | a | 1714m 1694s | 1620s 1594s 1570s 1544s 1510m | 1470—1462s 1438s 1410s 1390m 1350s 1272m 1220s | 1002s 914m 878m 864m 800m 784m |
| 24 | Cl | NHAc | H | a | 1702s | 1620—1590s 1534s 1508m | 1470—1462s 1438m 1408s 1384m 1350—1340s 1250m 1220s | 1040m 1006s 976m 932m 898w 870w 838w 800s 780w |
| 25 | H | NHBz | H | a | 1698s | 1620—1580s 1538s 1504s 1494m | 1470—1462s 1425s 1385m 1372s 1328s 1245m 1220s | 1085m 1064m 1044m 1030m 1016m 990s 935w 920m 900w 865w 820s 792m |
| 26 | Cl | NHBz | H | a | 1698s | 1616—1590s 1575s 1536s 1508m 1494m | 1470—1462s 1436m 1418—1404s 1384m 1346s 1244m 1218s | 1028m 1000s 970m 918w 898w 876w 840w 800—798s 772w |
| 27 | Cl | Cl | H | g | 1710s 1680s | 1616—1592s 1508s | 1470—1462s 1438m 1416—1405s 1384w 1350s 1244m 1220s | 1068w 1000m 980w 968w 925w 890w 814m 798m |
| 28 | Cl | Br | H | g | 1710s 1680s | 1616—1502s 1508s | 1470—1462s 1438m 1415—1406s 1384w 1350s 1245m 1220s | 1000m 798—785m |
| 29 | Cl | I | H | g | 1710s 1676s | 1616s 1592s 1508s | 1470—1462s 1438s 1416—1406s 1386m 1350s 1242m 1220s | 1068m 1000s 972w 928w 890w 800m 780m |

Refs.: (a) Ref. 4. (f) Ref. 5. (g) Walker, Warburton, and Webb, *J.*, 1962, 1277.

TABLE 3.

Absorption bands for 5- and 3′-substituted griseofulvic acid ($CHBr_3$ solution).

| Compound (II) | | | | | | Absorption bands (cm.$^{-1}$) | | | |
|---|---|---|---|---|---|---|---|---|---|
| No. | R | R′ | R″ | R‴ | Ref. | C=O stretching | C=C stretching | 1490—1210 | 1090—730 |
| 30 | Cl | Cl | H | H | g | 1742w 1710s 1662w | 1610—1600s 1576s | 1472—1462s 1420s 1386s 1348m 1278s 1250s 1230s | * |
| 31 | Br | Cl | H | H | g | 1740w 1710s 1675w | 1600s 1572s | 1470—1462s 1418s 1384s 1350m 1276m 1246s 1228s | 1060m 1012m 970s 950m 924m 846w 790w |
| 32 | Cl | Cl | Cl | H | g | 1716s 1687s | 1612s 1576s | 1476s 1460m 1420—1410s 1388s 1352m 1280m 1236—1224s | 1034w 1018w 976m 956m 925w 894w 820s 806m 790w |
| 33 | Br | Cl | Br | H | g | 1714s 1685s | 1608s 1572s | 1474—1460s 1420—1410s 1386s 1350w 1280m 1236—1222s | 1034w 1018m 978m 950m 928m 888w 812m 782m |
| 34 | Cl | Cl | Cl | Cl | g | 1760m 1742s 1702s | 1604s 1568s | 1474s 1460m 1418s 1385s 1348w 1280m 1234s 1220s | 1060m 1015w 970m 950m 912w 892w 878w 822m 802m 782m 762m |
| 35 | Br | Cl | Br | Br | g | 1735s 1702s | 1600s 1570s | 1472—1460s 1416s 1383s 1346m 1278s 1260s 1238s 1220s | 1078s 1048m 1022m 1008m 986m 976m 960w 942m 900w 864w 798m 772m |
| 36 | $NO_2$ | Cl | H | H | a | 1742m 1708s 1662s | 1620—1607s 1574s—1540s | 1486s 1460—1455m 1428s 1418m 1394m 1368s 1236—1230s | 1062s 1028m 972m 952m 918w 902w 886w 850w 842w |
| 37 | NHBz | H | H | H | a | 1742m 1690s 1664m | 1612—1600s 1510—1505m | 1490s 1442m 1418m 1384w 1354m 1266s | 1030m 1002w 956w 926w 914w 854w 810m |

Refs.: see Table 2.

TABLE 4.

Absorption bands for 2′,4′-bisethyleneketals of griseofulvic and of dechlorogriseofulvic acid analogues ($CHBr_3$ solution).

| Compound (III) | | | | | Absorption bands (cm.$^{-1}$) | | | |
|---|---|---|---|---|---|---|---|---|
| No. | R | R′ | R″ | Ref. | C=O stretching | C=C stretching | 1490—1210 | 1090—730 |
| 38 | OH | MeO | H | a | 1672s 1644s | 1612s 1500m | 1484s 1464s 1444m 1420w 1382w 1362s 1350—1338s 1276w 1235m 1210s | 1076s 1044m 1028m 998s 948m 906w 868w 832s 824m 800m |
| 39 | MeO | MeO | H | a | 1695s | 1620s 1600s 1506s | 1468—1460s 1438s 1430s 1384m 1370s 1350s 1338s 1324s 1270m 1245s 1220s | 1074s 1038s 1002s 950m 902w 878w 860w 828m 816s 793m |
| 40 | OH | MeO | Cl | b | 1674s 1644s | 1614s 1500m | 1468s 1435s 1384w 1362s 1336s 1320s 1275w 1238s | 1074s 1043s 1000s 972w 947m 894m 880w 842m 812m 788w 776w |
| 41 | MeO | OH | Cl | b | 1698s | 1618s 1598s 1508m | 1464m 1448m 1435m 1418m 1362s 1345m 1252s 1215s | 1074s 1054m 1045m 1000s 983m 948m 908w 880w 842m 812m 787m |
| 42 | MeO | MeO | Cl | b | 1694s | 1618—1590s 1506m | 1468—1460s 1438s 1416s 1382w 1350s 1270w 1243m 1218s | 1072s 1040s 1003s 980m 952m 906w 884—874w 838m 796s 780m |
| 43 | MeS | MeS | Cl | e | 1694s | 1585s 1555s 1508w | 1454s 1445—1430s 1380s 1364m 1350w 1332m 1276w 1250m 1236s | 1074s 1046s 1000s 980s 950s 926m 906w 880w 848w 812w 798m 776w 766m |
| 44 | $NH_2$ | MeO | Cl | e | 1682s | 1630—1615s 1585s 1500m | 1470s 1458s 1430s 1386s 1368s 1358m 1350m 1334m 1276—1260s 1224s | 1074s 1044s 1002s 954—944m 906w 892m 876w 842m 800s 784m |
| 45 | NHAc | MeO | Cl | e | 1702s 1672s | 1628s 1608s 1528s 1500m | 1468s 1452s 1406s 1384m 1368m 1350s 1326s 1256s 1212s | 1072s 1042s 1002s 970m 958m 946m 905w 894m 875w 838m 794w 780m |
| 46 | $PhCH_2{\cdot}NH$ | MeO | Cl | e | 1666s | 1628s 1606s 1514s 1500m | 1470—1460s 1446m 1416s 1386m 1360m 1344s 1235s | 1078s 1040m 1004s 950m 904w 880w 842w 790m |
| 47 | Pyrrolidin-1-yl | MeO | Cl | e | 1684s | 1620s 1555s 1508s | 1470—1455s 1420m 1382m 1365m 1354s 1264s 1232s | 1074s 1044m 1008s 975w 962w 945m 912—905m 876w 842w 824m 786—776m |

Refs.: see Table 1.

not have such a profound effect as that shown in the corresponding derivatives of griseofulvin and isogriseofulvin. Introduction of either a second alkyl or a second halogen group at carbon 3′ (*e.g.*, II; R = H, R′ = Cl, R″ = R‴ = Me) prevents enolisation in ring C and permits β-interaction between the 3- and the 2′-ketone groups; this effect is indicated by the appearance of carbonyl bands at 1742—1732 and 1702—1685 cm.$^{-1}$ (see Tables 2 and 3).

3′-Acetamidogriseofulvic acid (II; R = R‴ = H, R′ = Cl, R″ = NHAc), 3′-benzamidogriseofulvic acid (II; R = R‴ = H, R′ = Cl, R″ = NHBz), and 3′-benzamidodechlorogriseofulvic acid (II; R = R′ = R‴ = H, R″ = NHBz) in bromoform solution all show a nitrogen–hydrogen stretching band at 3350 cm.$^{-1}$ and strong secondary amide bands at 1620 and 1538—1534 cm.$^{-1}$. In the 3′-acetamido- and the 3′-benzamido-derivative of griseofulvin and the 3′-benzamido-derivative of isogriseofulvin,[4] however, the nitrogen–hydrogen band appears at 3350 cm.$^{-1}$, but the amide bands are displaced to 1700—1680 and 1496—1486 cm.$^{-1}$. This difference in behaviour may be attributed to enolisation in ring C of the griseofulvic acid derivatives; the enolic hydroxyl forms a hydrogen bond on to the carbonyl of the 3′-amide group and lowers the amide-carbonyl frequency to about 1620 cm.$^{-1}$. In the griseofulvin and isogriseofulvin derivatives, hydrogen bonding cannot occur, and the amide-carbonyl group therefore absorbs at a higher frequency, namely, 1700—1680 cm.$^{-1}$.

When examined in the solid state as Nujol mulls, griseofulvic acid and its derivatives unexpectedly gave three types of spectrum. The first type, which was given by griseofulvic acid and its 4,6-dialkoxy-analogues and by 3′-alkyl derivatives of griseofulvic acid, is characterised by a hydroxyl band at about 3300 cm.$^{-1}$ and by carbonyl bands between 1680 and 1650 cm.$^{-1}$. The 2′-ketone probably enolises, and the hydrogen atom of the resulting 2′-hydroxyl group bonds on to the 3-ketone, which then absorbs at 1680—1670 cm.$^{-1}$. The carbonyl stretching band for the 4′-ketone is displaced to about 1650 cm.$^{-1}$ by conjugate chelation with the 2′-ethylenic linkage.

Spectra of the second type are shown by compounds, such as 3′,3′-dialkyl- and 3′,3′-dihalogeno-griseofulvic acids, in which ring C is unable to enolise; the carbonyl bands, thanks to β-interaction between the 3- and the 2′-ketone group, appear at 1735—1726 and 1702—1680 cm.$^{-1}$. In the third type, of which 5-chloro- and 5-bromo-griseofulvic acid (II; R = R′ = Hal, R″ = R‴ = H) and a polymorphic form of 3′-methylgriseofulvic acid[5] are examples, the 3-ketone absorbs normally at about 1715 cm.$^{-1}$, but the absorption for the unenolised ketone in ring C (probably the 2′-ketone) is displaced to 1600—1550 cm.$^{-1}$ by conjugation and very strong hydrogen-bonding on to the hydroxyl group of the enolised 4′-ketone; strong hydrogen-bonding, probably dimerisation, is confirmed by the appearance of a displaced hydroxyl band at 2600 cm.$^{-1}$. Compounds giving the third type of spectrum behave normally in bromoform solution. The two polymorphic forms of 3′-methylgriseofulvic acid, which as Nujol mulls give type 1 and type 3 spectra, yield identical spectra when examined as solutions in bromoform or tetrahydrofuran.

The infrared spectrum of a pressed potassium chloride disc of griseofulvic acid frequently differs from that of a Nujol mull in showing a sharp band of variable intensity at about 1700 cm.$^{-1}$.[6] The band appears more readily in damp specimens of griseofulvic acid and is prominent in the spectra of samples that have been ground with potassium chloride for several minutes. Since we were unable to induce the band in a Nujol mull spectrum of griseofulvic acid, we believe that it is an artifact caused by partial formation of the potassium salt when griseofulvic acid is pressed with potassium chloride. A specimen of the sodium salt of griseofulvic acid prepared by titrating griseofulvic acid with sodium hydroxide, evaporating, and drying, absorbed at 1700 cm.$^{-1}$. This observation draws attention to a possible hazard in studying halide disc spectra.

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[4] Arkley, Gregory, and Walker, *J.*, 1963, 1603.

[5] Gregory, Holton, Robinson, and Walker, *J.*, 1962, 1269.

[6] Day, Nabney, and Scott, *J.*, 1961, 4067.

The 3-ketones of the 2′,4′-bisethylene ketals of griseofulvic acid (III; $R = R' = MeO$, $R'' = Cl$), dechlorogriseofulvic acid (III; $R = R' = MeO$, $R'' = H$), and the 4,6-dimethylthio-analogue of griseofulvic acid (III; $R = R' = MeS$, $R'' = Cl$) in bromoform solution absorb at 1695—1693 cm.$^{-1}$ (see Table 4). The 3-ketone in the 4-hydroxyl analogue of the bisethylene ketal (III; $R = HO$, $R' = MeO$, $R'' = Cl$) of griseofulvic acid, however, thanks to intramolecular hydrogen-bonding [7] on to the 4-hydroxyl group, absorbs at 1680—1672 cm.$^{-1}$; the 3-ketone group in the isomeric 6-hydroxyl analogue (III; $R = MeO$, $R' = HO$, $R'' = Cl$) cannot form a hydrogen bond on to the 6-hydroxyl group and accordingly absorbs at 1700 cm.$^{-1}$. The 4-amino- and 4-benzylamino-analogues behave similarly to the 4-hydroxyl analogue.

C=C *Stretching Bands*.—The bands at about 1615—1590 cm.$^{-1}$ and at 1508 cm.$^{-1}$ in the infrared spectrum of griseofulvic acid are C=C skeletal in-plane vibrations of aromatic ring A and appear in the spectra of all griseofulvic acid analogues (Tables 1—4) that have a 5-hydrogen atom. The 1615—1590 cm.$^{-1}$ bands resemble those of griseofulvin and isogriseofulvin in being considerably stronger than the corresponding carbonyl bands; they are only slightly affected by the introduction of either a 3′-alkyl or a 3′-halogen group or by the formation of a 2′,4′-bisethylene ketal.

TABLE 5.

Absorption bands for 2′-substituted analogues of griseofulvin and 4′-substituted analogues of isogriseofulvin ($CHBr_3$ solution).

| Compound | | | | Absorption bands (cm.$^{-1}$) | |
|---|---|---|---|---|---|
| No. | | R | Ref. | C=O stretching | C=C stretching |
| **48** | IV | H | h | 1708 1695 1675 | 1615—1595 1508 |
| **49** | V | H | h | 1696 1684 | 1616—1594 1506 |
| 50 | IV | Cl | h | 1706 1684 | 1614 1592 1506 |
| 51 | V | Cl | h | 1705 1684 | 1614 1590 1506 |
| 52 | IV | MeO | h | 1705 1654 | 1615—1591 1508 |
| 53 | V | MeO | h | 1698 1660 | 1614—1598 1510 |
| 54 | IV | MeS | h | 1706 1648 | 1614 1590 1570 1508 |
| 55 | V | MeS | h | 1695 1654 | 1614 1590 1572 1508 |
| 56 | IV | Pyrrolidin-1-yl | e | 1705 1610 | 1610—1590 1552 1508 |
| 57 | V | Pyrrolidin-1-yl | e | 1693 1620 | 1620—1595 1565—1555 1508 |
| 58 | V | Piperidino | e | 1692 1620 | 1620—1595 1552 1508 |
| 59 | V | Morpholino | e | 1696 1616 | 1616 1562 1508 |

The following analogues were also examined:

(Ref. i) (IV: $R = NH_2$ or $NH{\cdot}CH_2{\cdot}CH_2{\cdot}NEt_2$); (V: $R = NH_2$ or $NH{\cdot}CH_2{\cdot}CH_2{\cdot}NEt_2$).
(Ref. e) (IV: $R =$ NHMe or NHEt); (V: $R =$ NHMe, $NEt_2$, $NHBu^n$, or $NMe{\cdot}CH_2{\cdot}CH_2{\cdot}NEt_2$).

Refs.: (h) Ref. 1. (e) See Table 1. (i) Stephenson, Walker, Warburton, and Webb, *J.*, 1962, 1282.

Replacement of the 6-methoxyl group of griseofulvic acid by hydroxyl does not affect the frequency, but lowers the intensity of the 1615—1590 cm.$^{-1}$ C=C bands (Table 1); replacement of the 4-methoxyl group by hydroxyl not only weakens the 1615—1590 cm.$^{-1}$ bands, but also displaces them to 1614—1600 cm.$^{-1}$. This weakening of the 1615—1590 cm.$^{-1}$ bands accords with our suggestion [1] that their exceptionally high intensity in griseofulvin and its 4,6-dialkoxyl analogues is associated with the keto–enol ether system.

Greater changes occur in the 1600—1500 cm.$^{-1}$ region when the 4- and the 6-methoxyl group of griseofulvic acid and of its bisethylene ketal are replaced by alkylthio- or pyrrolidin-1-yl groups (Tables 1 and 4); a strong band appears near 1550 cm.$^{-1}$. Bromoform solution spectra of griseofulvin and isogriseofulvin analogues (see ref. 1 and Table 5), in which the 2′- or 4′-methoxyl group, respectively, are replaced by alkylthio-, piperidino-, pyrrolidin-1-yl, or morpholino-groups also show bands between 1572 and 1552 cm.$^{-1}$. Since the 4′- and the 2′-ketone group in these analogues absorb at much lower frequencies (1654—1610 cm.$^{-1}$) than those in griseofulvin and isogriseofulvin (1660—1654 cm.$^{-1}$), we

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[7] Boothroyd, Napier, and Somerfield, *Biochem. J.*, 1961, **80**, 34.

believe that the 1572—1552 cm.$^{-1}$ bands in these spectra are associated with C=C stretching of the 2′- and 3′-ethylenic linkages. However, when the 2′-pyrrolidin-1-yl analogue of griseofulvin and the 4′-pyrrolidin-1-yl analogue of isogriseofulvin were examined in different solvents,[1,8] we were surprised to find that the 1705—1693 cm.$^{-1}$ carbonyl bands and the 1565—1552 cm.$^{-1}$ C=C stretching bands were both sensitive to solvent change; this contrasted with our observations on griseofulvin and isogriseofulvin.[1]

The 1550 cm.$^{-1}$ bands in the spectra of the 4-pyrrolidin-1-yl and the 4,6-dialkylthio-analogues of griseofulvic acid and of its bisethylene ketal (Tables 1 and 4) probably represent C=C stretching of the aromatic ring, but are otherwise similar in origin to the 1572—1552 cm.$^{-1}$ bands of the griseofulvin analogues. The unusual position and the high intensity of these C=C bands appear to be characteristic of a basic substituent conjugated with a ketone.

The aromatic band at 1508 cm.$^{-1}$, of medium intensity, in the spectrum of griseofulvic acid disappears if either a 5-halogen or a 5-nitro-group is introduced (see Table 3). Introduction of a 4-hydroxy-, 4-amino-, 4-acetamido-, or 4-benzylamine-group, but not of a 4-methylthio- or a 4-pyrrolidin-1-yl group, displaces the 1508 cm.$^{-1}$ band to about 1500 cm.$^{-1}$ (see Table 4).

*Carbon–Hydrogen Deformation Bands.*—The carbon–hydrogen deformation bands that appear between 1480 and 1350 cm.$^{-1}$ in the spectra of griseofulvic acid analogues (see Table 1), in general, accord with those that we reported for griseofulvin. The bands for the 2′-oxo-4′-enol and 4′-oxo-2′-enol ether systems are absent, but those for the 4- and 6-alkoxyl groups can be identified. The 4,6-dimethylthio-analogues do not show the 1470—1462 cm.$^{-1}$ band that we assigned to asymmetrical $CH_3$ bending of the methoxy-group, but absorb instead at 1454—1452 cm.$^{-1}$. Similar absorption is shown by the 4,6-dimethylthio-analogues of griseofulvin and isogriseofulvin, and we have therefore assigned this band to asymmetrical $CH_3$ bending of the methylthio-group; the corresponding symmetrical band probably appears at about 1430 cm.$^{-1}$.

*Carbon–Oxygen Stretching Bands.*—Griseofulvic acid, its sodium salt, and its 4,6-dialkoxyl analogues, when examined as Nujol mulls, show strong carbon–oxygen stretching bands at about 1358, 1225, 1145, and 1102 cm.$^{-1}$. These bands are somewhat similar to those shown by griseofulvin and 4′-oxo-2′-enol ethers; isogriseofulvin and 2′-oxo-4′-enol ethers can be distinguished by additional bands at 1388 and 1175 cm.$^{-1}$ of medium intensity.

The 2′,4′-bisethylene ketals of griseofulvic acid and of its 4,6-dialkoxyl analogues, when examined as Nujol mulls, show besides the alkoxyl C–O stretching bands at about 1358, 1225, 1135, and 1102 cm.$^{-1}$, additional adsorption at about 1135 and 1070 cm.$^{-1}$ for the ketal linkages. The C–O bands for methoxyl groups are readily distinguished from those for the ketals by comparing the carbon disulphide solution spectrum of the 2′,4′-bisethylene ketal of griseofulvic acid (III; $R = R' = MeO$, $R'' = Cl$) with that of its 4,6-dimethylthio-analogue (III; $R = R' = MeS$, $R'' = Cl$). The bands at about 1354, 1220, 1138, and 1110 cm.$^{-1}$ are associated with the methoxyl groups and those at 1120—1110 and 1080—1078 cm.$^{-1}$ with the ethylene ketals. This agrees with our observation that the C–O stretching bands for the 3-ethylene ketal of cholestan-3-one appear at 1136, 1108, 1094, and 1074 cm.$^{-1}$, compared with 1190—1175, 1155—1132, 1110—1100, and 1053—1050 cm.$^{-1}$ for 3,3-dialkoxy-steroids;[9] the 1108 and 1094 cm.$^{-1}$ bands for the 3-ethylene ketal are considerably stronger than the 1136 and 1074 cm.$^{-1}$ bands, whereas the 1190—1175 and 1155—1132 bands for 3,3-dialkoxy-steroids are weaker than those at 1110—1100 and 1053—1050 cm.$^{-1}$.

The absorption bands shown by griseofulvic acid and its analogues in the 1000—650 cm.$^{-1}$ region are consistent with those reported in our study of griseofulvin and isogriseofulvin.[1]

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

[9] Bergmann and Pinchas, *Rec. Trav. chim.*, 1952, **71**, 1611; Page, *J.*, 1955, 2017

*Experimental.*—The griseofulvic acid analogues were examined over the 4000—650 cm.$^{-1}$ spectral region as Nujol mulls and, whenever the compounds were sufficiently soluble, as 1·0% w/v solutions in bromoform, stabilised with 0·05% of diphenylamine, in 0·8 mm. cells, by means of a Perkin-Elmer Corporation model 21, double-beam infrared spectrophotometer fitted with a sodium chloride prism. The more soluble 2′,4′-bisethylene ketals were also studied as 1·0% w/v solutions in carbon disulphide in 0·8 mm. cells, but the less soluble griseofulvic acids were examined as saturated bromoform solutions ($<$0·1% w/v) in 0·8 mm. cells in a spectrophotometer fitted with ordinate scale expansion; special care was taken to remove suspended material. Several compounds were also studied as either potassium chloride discs or 2·5% w/v tetrahydrofuran solutions in 0·1 mm. cells.

All the compounds were prepared in these laboratories and had the physical properties described in the references listed in the Tables.

The spectra of a selection of these compounds have been allotted nos. 10,600—10,615 in the D.M.S. Scheme (Butterworths Scientific Publications, London).

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