241. *Griseofulvin Analogues. Part I. Modification of the Aromatic Ring.*

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Alkylation of the phenol (I; R = R″ = Me, R′ = H) gave modifications of isogriseofulvin (I; R = R′ = R″ = Me) with a variety of alkoxy-substituents at position 6. Acid hydrolysis gave the acids (II; R′ = Me, R = Alkyl) from which the griseofulvin derivatives (III; R = R″ = Me, R′ = Alkyl) were prepared by methylation. Griseofulvin (III; R = R′ = R″ = Me) with magnesium iodide in ether gave the phenol (III; R = R′ = Me, R″ = H), which was a useful starting material for analogues with modified substituents at position 4.

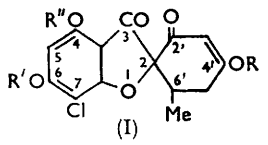
THE mould metabolite griseofulvin (III; R = R′ = R″ = Me) is now widely used for oral treatment of human fungal infections.[1] Analogues of griseofulvin, prepared for an investigation of the relation between structure and biological activity, are described in this and subsequent papers.

Under certain conditions, metabolism of griseofulvin involves demethylation of the methoxy-groups of the aromatic ring. In some mammals and man, the biologically inactive phenol[2] (III; R = R″ = Me, R′ = H) is the major product, whereas *Microsporum canis*[3] metabolises griseofulvin to the 4-phenol (III; R = R′ = Me, R″ = H). Other micro-organisms[3] produce both these phenols together with griseofulvic acid (II; R = R′ = Me).

An obvious starting material for the preparation of 6-alkoxy-analogues of griseofulvin is the phenol (II; R = H, R′ = Me) (norgriseofulvic acid) prepared[4] by alkaline hydrolysis of griseofulvic acid; improved conditions for the hydrolysis of griseofulvin to griseofulvic acid are given in the Experimental section. The low yield in this hydrolysis was not improved, in spite of changes in the pH, the major by-product being the dibenzofuran (IV)

[1] Blank, *Arch. Dermatology*, 1960, **81**, No. 5; *Trans. St. John's Hospital Dermatol. Soc.*, 1960, No. 45.
[2] Barnes and Boothroyd, *Biochem. J.*, 1961, **78**, 41.
[3] Boothroyd, Napier, and Somerfield, *Biochem. J.*, 1961, **80**, 34.
[4] Grove, MacMillan, Mulholland, and Rogers, *J.*, 1952, 3949.

arising from rupture of the β-diketone with subsequent ring-closure.[5] In order to inhibit this degradation we decided to protect ring c by forming the bisethylene ketal (V; R = R′ = Me). Griseofulvin and griseofulvic acid (II; R = R′ = Me) were converted into their bisethylene ketals by reaction with ethane-1,2-diol in the presence of the boron trifluoride–ether complex [6] or pyridine hydrochloride.[7] Selective hydrolysis in aqueous acetic acid gave the 2′-ketal (VI; R = R′ = Me), attack taking place at the less hindered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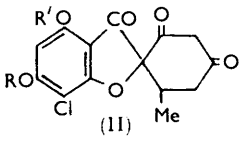
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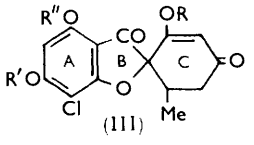
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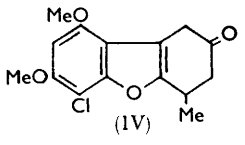
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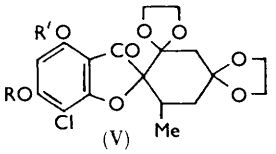
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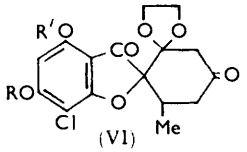
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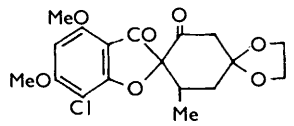

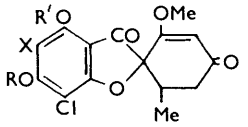
(VIII)

4′-position. The corresponding 4′-ketal (VII) was obtained, in low yield, during ketalisation of the trione (II; R = R′ = Me) in presence of pyridine hydrochloride. It was distinguished from the 2′-ketal by a characteristic band at *ca.* 1730 cm.$^{-1}$ in the infrared spectrum (associated with interaction between the 2′- and the 3-carbonyl groups). A similar effect has been observed with other compounds.[8] Hydrolysis of all these ketals with mineral acid regenerated griseofulvic acid (II; R = R′ = Me). Attempts to hydrolyse the bisketal with aqueous alkali were unsuccessful; it appears that ketalisation of the carbonyl system in ring c of griseofulvin stabilises the 6-methoxy-group. Earlier workers [9] have shown that the 7-chlorine atom also affected the stability of the 6-methoxy-group, for dechlorogriseofulvin could not be hydrolysed to the corresponding 6-phenol. 7-Chloro-2′,4′-bisethylenedioxy-6-hydroxy-4-methoxy-6′-methylgrisan-3-one (V; R = H, R′ = Me) was prepared by direct ketalisation of the phenol (I; R = R″ = Me, R′ = H). Selective acid hydrolysis then gave the 2′-ketal (VI; R = H, R′ = Me).

To prevent the possibility of *C*-alkylation at position 3′ during etherification of the 6-hydroxy-group, the trione (II; R = H, R′ = Me) was converted into the 4′-methyl ether (I; R = R″ = Me, R′ = H) by acid-catalysed methylation; [10] the phenolic hydroxyl group was not alkylated under these conditions. This phenol was readily methylated or ethylated with the corresponding diazoalkane. The higher 6-alkyl ethers were prepared by alkylation of the phenol with a halide in presence of silver oxide,[11] or, with the more reactive benzyl or allyl halide, in presence of potassium carbonate.[12] These ethers (I; R = R″ = Me, R′ = Alkyl) were converted into the required griseofulvin analogues by acid hydrolysis and methylation of the resulting triones or their more soluble triethylamine salts [13] (II; R′ = Me, R = Alkyl) with diazomethane. Alternatively, ring-c enol ethers

[5] Grove, MacMillan, Mulholland, and Rogers, *J.*, 1952, 3977.
[6] Fieser, *J. Amer. Chem. Soc.*, 1954, 1945.
[7] Rosenkranz, Kaufmann, and Romo, *J. Amer. Chem. Soc.*, 1949, **71**, 3689.
[8] Mulholland, *J.*, 1952, 3987, 3994.
[9] MacMillan, *J.*, 1953, 1697.
[10] Duncanson, Grove, and Jeffs, *J.*, 1958, 2929.
[11] Purdie and Irvine, *J.*, 1903, **83**, 1021.
[12] Claisen, *Annalen*, 1918, **418**, 69; Auwers, *Ber.*, 1938, **71**, 2082.
[13] Frankel and Katchalski, *J. Amer. Chem. Soc.*, 1944, **66**, 763.

were prepared by base-catalysed alkylation as described above. The 2'- and 4'-ethers so obtained were separated by chromatography on alumina;[10] alternatively, the 2'-ether was separated by means of its water-soluble Girard-P derivative.

The 6-benzyl ether (III; R = R'' = Me, R' = CH_2Ph) was hydrogenated in presence of palladium, to give the important biological metabolite of griseofulvin, 7-chloro-6-hydroxy-4,2'-dimethoxy-6'-methylgris-2'-en-3,4'-dione (III; R = R'' = Me, R' = H).

In order to prepare a range of 4-ethers of griseofulvin, the phenol (III; R = R' = Me, R'' = H) was required. Attempts to prepare it by selective demethylation of griseofulvin with hydrobromic acid,[14] aluminium chloride,[15] stannic chloride,[16] or lithium iodide [17] were unsuccessful, but some was isolated during an investigation [18] of the action of Grignard reagents on griseofulvin. Demethylation with Grignard reagents has been widely reported,[19] and early workers [20] had attributed the demethylation to the presence of magnesium iodide in the reagent. We found that the magnesium iodide–ether complex smoothly demethylated griseofulvin to the required phenol; magnesium bromide was much less successful.

Surprisingly, the hydrogen-bonded 4-phenol (III; R = R' = Me, R'' = H) was more readily alkylated by the Claisen method [12] than was the 6-phenol (I; R = R'' = Me, R' = H), and several alkyl ethers were prepared from it.

For part of the work we required analogues of griseofulvin with a basic side-chain attached at the 4- or the 6-position. Alkylation of the corresponding phenols with amino-alkyl halides in the presence of potassium carbonate was limited to stable [21] 2-dialkylamino-ethyl halides. A similar limitation applied to the use of amides $R_2N{\cdot}[CH_2]_n{\cdot}NH{\cdot}CO{\cdot}CH_2Cl$. The 4-oxyacetic acid analogue (III; R = R' = Me, R'' = $CH_2{\cdot}CO_2H$) of griseofulvin, prepared from the 4-phenol by etherification with benzyl bromoacetate and hydrogenolysis of the benzyl ester, was condensed with bases of the type $R_2N{\cdot}[CH_2]_n{\cdot}NH_2$ in the presence of dicyclohexylcarbodi-imide [22] or ethoxyacetylene [23] to give the corresponding amides. Preparation of such amides through the mixed anhydride [24] of the acid (III; R = R' = Me, R'' = $CH_2{\cdot}CO_2H$) with ethyl chloroformate was not achieved and attempts to prepare the acid chloride (III; R = R' = Me, R'' = $CH_2{\cdot}COCl$) failed.

Finally, some 5-substituted analogues of griseofulvin were prepared. Rearrangement of the 4-allyl ether (III; R = R' = Me, R'' = $CH_2{:}CH{\cdot}CH_2$), under standard conditions,[25] gave the 5-allyl phenol (VIII; R = Me, R' = H, X = $CH_2{:}CH{\cdot}CH_2$), and subsequent methylation provided the 5-allyl analogue (VIII; R = R' = Me, X = $CH_2{:}CH{\cdot}CH_2$) of griseofulvin; this was hydrogenated to give 5-propylgriseofulvin (VIII; R = R' = Me, X = Pr^n).

Attempts to prepare a 5-acetyl analogue (VIII; R = R' = Me, X = Ac) by Fries rearrangement of the 4- or the 6-acetoxy-compound (III; R = R' = Me, R'' = Ac; or I; R = R'' = Me, R' = Ac) with boron trifluoride–ether resulted only in regeneration of the phenol.

The infrared spectra of these compounds will be discussed in Part V of this series (p. 1292).

[14] Stoermer, *Ber.*, 1908, **41**, 321.
[15] Aiyar, Dass, and Seshadri, *Proc. Indian Acad. Sci.*, 1957, **46**, *A*, 238.
[16] Stadnikoff and Goldfarb, *Ber.*, 1928, **61**, 2341.
[17] Taschner and Liberek, *Roczniki Chem.*, 1956, **30**, 323; Elsinger, Schreiber, and Eschenmoser, *Helv. Chim. Acta*, 1960, **43**, 113.
[18] Hunt and Peel, personal communication.
[19] Grignard, *Compt. rend.*, 1910, **151**, 322.
[20] Schönberg and Moubasher, *J.*, 1944, 462.
[21] Littmann and Marvel, *J. Amer. Chem. Soc.*, 1930, **52**, 287.
[22] Sheehan and Hess, *J. Amer. Chem. Soc.*, 1955, **77**, 1067.
[23] Arens, *Rec. Trav. chim.*, 1955, **74**, 769.
[24] Vaughan and Osato, *J. Amer. Chem. Soc.*, 1952, **74**, 676; Boissonnas, *Helv. Chim. Acta*, 1951, **34**, 874; Wieland and Bernhard, *Annalen*, 1951, **572**, 190.
[25] Tarbell, " Organic Reactions," John Wiley and Sons, Inc., New York, 1944, Vol. II, p. 1.

Experimental

M. p.s were measured in capillary tubes and are corrected. Solvents (except when otherwise stated) were acetone for optical rotations, measured at 20—23° (concentration 1 ± 0·3%); ethanol for ultraviolet absorption spectra; bromoform for infrared spectra. Solutions in organic solvents were dried ($MgSO_4$) before evaporation. The alumina used for chromatography was Woelm pH 4 Brockmann grade II.

7-Chloro-4,6-dimethoxy-6'-methylgrisan-3,2',4'-trione (II; R = R' = Me).—2N-Sulphuric acid (50 ml.) was added to a solution of griseofulvin (50·0 g.) in acetic acid (250 ml.), and the mixture was heated on the steam-bath (45 min.). Crystals of the trione started to separate after 15 min. The mixture was cooled, and the product was collected, washed successively with methanol and ether, and dried to give griseofulvic acid (II; R = R' = Me) (44·2 g., 92%), m. p. 262—263° (decomp.), $[\alpha]_D$ +397° (*c* 1·02 as Na salt in aq. MeOH), $\lambda_{max.}$ (in 0·1N-NaOH) ~234 (ε 12,300), 288 (ε 44,600), and 324 mμ (ε 6300), $\nu_{max.}$ (in Nujol) 3250 (OH), 1676 and 1660 (CO·C:C), 1235 and 1225 $cm.^{-1}$ (aromatic ether).

7-Chloro-6-hydroxy-4,4'-dimethoxy-6'-methylgris-3'-en-3,2'-dione (I; R = R'' = Me, R' = H).—Griseofulvic acid (II; R = R' = Me) (150 g.) was stirred and boiled under reflux with 0·5N-sodium hydroxide (3 l.) for 5 hr. The solution was cooled, and the precipitated dibenzofuran (IV) was removed by filtration (50·5 g., 39%). When crystallised from alcohol, it had m. p. 137—138°, $[\alpha]_D$ −29°, $\lambda_{max.}$ 263 mμ (ε 15,000); Grove *et al.*[4] give m. p. 138°, $[\alpha]_D$ −29°. Acidification of the filtrate precipitated the crude trione (II; R = H, R' = Me) (80·9 g.) which was washed with water and dried *in vacuo*; coloured impurities were removed by washing with cold ethyl acetate. This material (55 g.) was boiled under reflux for 5 hr. with toluene-*p*-sulphonic acid (2·8 g.) and 2,2-dimethoxypropane (15·4 ml.) in dry methanol (1·1 l.). Most of the methanol was removed *in vacuo* and the residue was poured into 2N-sodium carbonate (1 l.). After being washed with chloroform (2 × 250 ml.), the alkaline layer was acidified with concentrated hydrochloric acid. The precipitate (50·9 g.; m. p. 253—269°) crystallised from methanol to give the *phenol* (I; R = R'' = Me, R' = H) (34·3 g., 23%), m. p. 269°, $[\alpha]_D$ +231°, $\lambda_{max.}$ (in 0·1N-NaOH) 287 (ε 26,600) and 323 mμ (ε 33,600), $\nu_{max.}$ (in Nujol) 1660 $cm.^{-1}$ (CO·C:C) (Found: C, 56·6; H, 4·5; Cl, 10·4; OMe, 18·0. $C_{16}H_{15}ClO_6$ requires C, 56·7; H, 4·5; Cl, 10·5; OMe 18·3%). The *acetate* (from ethanol) had m. p. 197—198°, $[\alpha]_D$ +162°, $\lambda_{max.}$ 225 (ε 18,350), 260—261 (ε 24,500), 278—282 (infl.) (ε 12,900), and 334 mμ (ε 5000) (Found: C, 56·8; H, 4·5; Cl, 9·4; OMe, 16·4. $C_{18}H_{17}ClO_7$ requires C, 56·8; H, 4·5; Cl, 9·3; OMe, 16·3%).

7-Chloro-4-hydroxy-6,2'-dimethoxy-6'-methylgris-2'-en-3,4'-dione (III; R = R' = Me, R'' = H).—A solution of magnesium iodide ether solvate, prepared from magnesium turnings (8·0 g.) and iodine (40 g.) in ether (50 ml.) and benzene (100 ml.), was filtered from the excess of magnesium and added dropwise to a stirred suspension of griseofulvin (56 g.) in benzene (2 l.). The mixture was then stirred and refluxed for 3 hr., cooled, and acidified with 0·5N-hydrochloric acid (800 ml.). The benzene layer was separated and shaken with 2N-sodium carbonate solution (800 ml.), and the mixture was filtered from the sparingly soluble sodium salt of the phenol. The benzene layer was again extracted with 2N-sodium carbonate (200 ml.). The combined sodium salt and aqueous alkaline extracts were acidified, and the precipitate was collected, washed with ether, and crystallised from aqueous acetic acid to give the 4-phenol (III; R = R' = Me, R'' = H) (44·9 g., 79%), m. p. 140—143°, $[\alpha]_D$ +322°, $\lambda_{max.}$ 236 (ε 22,000), 288 (ε 22,200), and 330 mμ (ε 3990), $\lambda_{max.}$ (in 0·1N NaOH) 241—243 (ε 25,550), 284—286 (ε 25,500), and 357—359 mμ (ε 7200), $\nu_{max.}$ 3500 (OH), 1684 (C=O), and 1654 $cm.^{-1}$ (CO·C:C) (Found: C, 53·8; H, 4·9; Cl, 10·0; OMe, 17·4. $C_{16}H_{15}ClO_6,H_2O$ requires C, 53·9; H, 4·8; Cl, 10·0; OMe, 17·4%). Drying this product at 100° *in vacuo* gave a lower-melting (117—119°) anhydrous form. It gave an *acetate* (from ethanol), m. p. 196—197°, $[\alpha]_D$ +246°, $\lambda_{max.}$ 239 (ε 30,400) and 288 mμ (ε 23,200) (Found: C, 57·1; H, 4·4; Cl, 9·1; OMe, 16·3. $C_{18}H_{17}ClO_7$ requires C, 56·8; H, 4·5; Cl, 9·3; OMe, 16·3%), *benzoate* (from ethanol), m. p. 184—185°, $[\alpha]_D$ +222°, $\lambda_{max.}$ 239 (ε 44,000) and 288 mμ (ε 20,900) (Found: C, 62·5; H, 4·4; Cl, 8·0; OMe, 14·8. $C_{23}H_{19}ClO_7$ requires C, 62·4; H, 4·3; Cl, 8·0; OMe, 14·0%), and *methanesulphonate* (from ethanol), m. p. 191°, $[\alpha]_D$ +224°, $\lambda_{max.}$ 238·5 (ε 28,900) and 288·5 mμ (ε 19,900) (Found: C, 49·2; H, 4·25; Cl, 8·5; S, 7·5; OMe, 15·1. $C_{17}H_{17}ClO_8S$ requires C, 49·0; H, 4·1; Cl, 8·5; S, 7·7; OMe, 14·9%). Mineral acid hydrolysed the phenol (III; R = R' = Me, R'' = H) to the *trione* (II; R = Me, R' = H) (88%); crystallised from aqueous acetic acid, this had m. p. 144° (decomp.), $[\alpha]_D$

+257°, $\lambda_{max.}$ 242 (ε 15,000), 286 (ε 44,100), and 362 mμ (ε 7450), $\nu_{max.}$ (in Nujol) 1670 cm.$^{-1}$ (bonded CO·C:C) (Found: C, 52·4; H, 4·6; Cl, 10·1; OMe, 9·3. $C_{15}H_{13}ClO_6,H_2O$ requires C, 52·5; H, 4·4; Cl, 10·4; OMe, 9·1%).

Application of the demethylation procedure to isogriseofulvin (I; R = R′ = R″ = Me) gave *7-chloro-4-hydroxy-6,4′-dimethoxy-6′-methylgris-3′-en-3,2′-dione* (I; R = R′ = Me, R″ = H) (89%), m. p. 127—133° (decomp.) (from aqueous acetic acid), $[\alpha]_D$ +212°, $\lambda_{max.}$ 235 (ε 21,800), 261 (ε 20,000), 288 (ε 19,900), and 328 mμ (ε 4300), $\nu_{max.}$ 3460 (bonded OH), 1664 (bonded C=O), and 1644 cm.$^{-1}$ (CO·C:C) (Found: C, 56·1; H, 4·5; Cl, 10·4; OMe, 17·8. $C_{16}H_{15}ClO_6,\frac{1}{2}H_2O$ requires C, 56·0; H, 4·6; Cl, 10·3; OMe, 18·1%).

7-Chloro-2′,4′-bisethylenedioxy-4,6-dimethoxy-6′-methylgrisan-3-one (V; R = R′ = Me).—(*a*) Griseofulvin (5·0 g.) was stirred and boiled under reflux for 16 hr. with dry ethane-1,2-diol (50 ml.) and pyridine hydrochloride [from pyridine (1 ml.) and hydrogen chloride in benzene (100 ml.)] in benzene (500 ml.). Water, formed during the reaction, was removed azeotropically in a Dean–Stark apparatus packed with magnesium sulphate. The cooled mixture was poured into water; the *bisketal* (V; R = R′ = Me) was isolated from the benzene layer and, crystallised from methanol (5·21 g., 93%), had m. p. 198—199°, $[\alpha]_D$ −98°, $\lambda_{max.}$ 288 (ε 22,300) and 324 mμ (ε 5400), $\nu_{max.}$ 1696 cm.$^{-1}$ (C=O) (Found: C, 56·1; H, 5·5; Cl, 8·5. $C_{20}H_{23}ClO_8$ requires C, 56·3; H, 5·4; Cl, 8·3%). This bisketal sometimes crystallised in a different form, m. p. 226°, with an identical infrared spectrum.

(*b*) Griseofulvin (500 g.) was stirred with redistilled ethane-1,2-diol (1250 ml.) and gently warmed. Boron trifluoride–ether complex was added rapidly, with stirring, until the mixture nearly solidified. Benzene (1 l.) was added and then more boron trifluoride–ether (total 500 ml.). The mixture was stirred for 1 hr. and then allowed to cool. Water (1 l.) was added and the mixture stirred. The solid was collected and was washed successively with water and light petroleum (b. p. 40—60°), giving the bisketal (464 g., 71%), m. p. 226°, $[\alpha]_D$ −100°. The aqueous filtrates were extracted with ethyl acetate (1 l.) and this extract was combined with the benzene layer, washed with water, evaporated, and triturated with ether to give the bisketal(85·7 g.), m. p. 226°, $[\alpha]_D$ −104°.

Hydrolysis with mineral acid. This bisketal (V; R = R′ = Me) (0·5 g.) was heated for 45 min. on the steam-bath with acetic acid (5 ml.) and 2N-sulphuric acid (1 ml.). On cooling, griseofulvic acid (II; R = R′ = Me) separated (0·31 g., 78%), having m. p. 265° (decomp.).

7-Chloro-2′-ethylenedioxy-4,6-dimethoxy-6′-methylgrisan-3,4′-dione (VI; R = R′ = Me).—The bisketal (V; R = R′ = Me) (50 g.) in acetic acid (375 ml.) was heated to 90—95° and treated with hot (90—95°) water (625 ml.) during 30 min. The solution was cooled, then poured into water (200 ml.), and the precipitated solid crystallised from methanol to give the *2′-ketal* (VI; R = R′ = Me) (27·0 g., 60%), m. p. 205—207°, $[\alpha]_D$ −147°, $\lambda_{max.}$ 233 (ε 14,200), 289 (ε 23,470), and 324 mμ (ε 5300), $\nu_{max.}$ 1694, 1716 cm.$^{-1}$ (ketones) (Found: C, 56·3; H, 4·7; Cl, 9·5. $C_{18}H_{19}ClO_7$ requires C, 56·5; H, 5·0; Cl, 9·3%).

7-Chloro-4′-ethylenedioxy-4,6-dimethoxy-6′-methylgrisan-3,2′-dione (VII).—Griseofulvic acid (5·0 g.) was stirred with ethane-1,2-diol (50 ml.) and pyridine hydrochloride (from 1·25 ml. of pyridine) in boiling benzene (500 ml.) for 17 hr. Water was removed azeotropically. The mixture was cooled and poured into water and the organic layer separated and washed with 2N-sodium carbonate (250 ml.) and water (250 ml.). Evaporation of the solvent *in vacuo* gave white crystals (2·53 g.), m. p. 188—191° depressed by 3° on admixture with the bisketal (V; R = R′ = Me). Trituration with methanol and crystallisation from ethyl acetate–light petroleum (b. p. 60—80°) gave the *4′-ketal* (VII) (0·5 g.), m. p. 260—263°, $[\alpha]_D$ +54°, $\lambda_{max.}$ 292 mμ (ε 22,700), $\nu_{max.}$ 1732, 1690 cm.$^{-1}$ (C=O) (Found: C, 56·8; H, 5·2; Cl, 9·2. $C_{18}H_{19}ClO_7$ requires C, 56·5; H, 5·0; Cl, 9·3%).

7-Chloro-2′,4′-bisethylenedioxy-6-hydroxy-4-methoxy-6′-methylgrisan-3-one (V; R = H, R′ = Me,) was prepared in 84% yield as in method (*a*) above, from the phenol (I; R = R″ = Me, R′ = H). When crystallised from methanol, it had m. p. 271—272°, $[\alpha]_D$ −94°, $\lambda_{max.}$ (in 0·1N-NaOH) 247 (ε 11,500) and 320 mμ (ε 45,000), $\nu_{max.}$ 1694 cm.$^{-1}$ (C=O) (Found: C, 55·3; H, 5·0; Cl, 8·6. $C_{19}H_{21}ClO_8$ requires C, 55·3; H, 5·1; Cl, 8·6%). Selective hydrolysis as described above gave *7-chloro-2′-ethylenedioxy-6-hydroxy-4-methoxy-6′-methylgrisan-3,4′-dione* (VI; R = H, R′ = CH_3), m. p. 218—221° (from EtOH), $[\alpha]_D$ −133°, $\lambda_{max.}$ (0·1N-NaOH) 249 (ε 11,400) and 324 mμ (ε 32,000), $\nu_{max.}$ 1720, 1696 cm.$^{-1}$ (ketones) (Found: C, 55·5; H, 4·8; Cl, 9·6. $C_{17}H_{17}ClO_7$ requires C, 55·4; H, 4·8; Cl, 9·6%).

7-Chloro-2′,4′-bisethylenedioxy-4-hydroxy-6-methoxy-6′-methylgrisan-3-one (V; R = Me, R′ =

H).—Ketalisation of the 4-phenol (III; R = R′ = Me, R″ = H) as described in method (*b*) above gave *compound* (V; R = Me, R′ = H), m. p. 249° (from EtOH), $[\alpha]_D$ −105°, $\lambda_{max.}$ 284—285 (ε 21,000) and 325 mμ (ε 4300), $\nu_{max.}$ 1676 cm.$^{-1}$ (bonded C=O) (Found: C, 55·0; H, 5·3; Cl, 8·6. $C_{19}H_{21}ClO_8$ requires C, 55·3; H, 5·1; Cl, 8·6%). This compound was also prepared, in 74% yield, by magnesium iodide demethylation of 7-chloro-2′,4′-bisethylenedioxy-4,6-dimethoxy-6′-methylgrisan-3-one (V; R = R′ = Me).

Preparation of Alkyl Ethers.—Method A. As a general procedure for the preparation of the 4-alkyl (III; R = R′ = Me, R″ = Alkyl) and 6-alkyl (I; R = R″ = Me, R′ = Alkyl) ethers, the corresponding phenol (5·0 g.) was heated under reflux for 18 hr. in acetone (125 ml.) with anhydrous potassium carbonate (15·0 g.) and the alkyl halide (1·1 mole; or, in the case of appreciably volatile halides, 10 ml.). The solution was cooled and filtered, and the residual salts were extracted with hot acetone (2 × 250 ml.). The combined acetone extracts were evaporated *in vacuo*, and the residue was dissolved in ethyl acetate (250 ml.) and washed successively with N-sodium carbonate solution (2 × 250 ml.) and water (2 × 100 ml.). Evaporation of the solvent gave the alkyl ether.

Method B. The 6-alkoxy-triones (II; R′ = Me, R = Alkyl) were prepared by heating a mixture of the phenol (I; R = R″ = Me, R′ = H) (10·0 g.) with silver oxide (16·5 g.) and the alkyl halide (20 ml.) in dry acetone (300 ml.) under reflux for 20 hr. The mixture was filtered, the residual salts were washed with acetone (200 ml.), and the combined acetone solutions were evaporated *in vacuo*. The gum was dissolved in ethyl acetate (500 ml.) and washed successively with N-sodium carbonate (2 × 250 ml.) and water (250 ml.). The solvent was removed and the crude 4′-methyl ether (I; R = R″ = Me, R′ = Alkyl) was hydrolysed by heating it on the steam-bath for 1 hr. with 2N-sulphuric acid (8 ml.) and acetic acid (40 ml.). When the solution was kept overnight the trione usually crystallised (dilution with water was sometimes necessary).

To prepare the corresponding 2′-methyl ethers (III; R = R″ = Me, R′ = Alkyl), the trione (4·0 g.) was dissolved in methanol or acetone in presence of triethylamine (1·1 mol.) and treated with an excess of ethereal diazomethane. Unchanged diazomethane was destroyed with acetic acid, and the mixture was evaporated *in vacuo*. The residue, in ethyl acetate (250 ml.), was extracted with N-sodium carbonate (2 × 250 ml.) and then water (250 ml.), and the solvent was evaporated. The mixed 2′- and 4′-methyl ethers were boiled in ethanol (36 ml.) and acetic acid (4 ml.) and under reflux for 30 min. with Girard's reagent P (2·0 g.). The mixture was cooled and poured into saturated sodium hydrogen carbonate solution (150 ml.) and water (300 ml.). Extraction with ethyl acetate gave the crude 4′-methyl ether (I; R = R″ = Me, R′ = Alkyl). The combined aqueous solutions were adjusted to pH 1 and stirred for 4 hr. with ethyl acetate (200 ml.). The ethyl acetate layer was separated, washed successively with saturated sodium hydrogen carbonate solution (200 ml.) and water (200 ml.) and evaporated, to give the 2′-methyl ether (III; R = R″ = Me, R′ = Alkyl). Alternatively the 2′- and the 4′-methyl ether were separated by chromatography on alumina, the 4′-ethers being eluted first, with ether–benzene mixtures. The 2′-ether was then obtained by elution with benzene containing methanol.

The properties of the analogues of griseofulvin are summarised in Tables 1—3. All the compounds in Tables 2 and 3 were crystallised from ethanol or aqueous ethanol. All compounds gave satisfactory alkoxyl analyses. The ultraviolet spectra of the triones (II; R′ = Me, R = Alkyl) were measured in 0·1N-sodium hydroxide and showed $\lambda_{max.}$ 290 mμ (ε ~40,000). The ultraviolet spectra of the analogues (III; R = R″ = Me, R′ = Alkyl) in Table 2 showed $\lambda_{max.}$ 236 (ε ~23,000), 292 (ε ~26,000), and 320 mμ (ε ~5500). The corresponding 4′-ethers (I; R = R″ = Me, R′ = Alkyl) in Table 3 showed $\lambda_{max.}$ 235 (ε ~22,000), 261 (ε ~21,000), 292 (ε ~21,000), and 324 mμ (ε ~5500).

In Table 1, the overall yield quoted refers to the etherification of the phenol (I; R = R″ = Me, R′ = H) and subsequent acid hydrolysis to the trione (II; R = Alkyl, R′ = Me).

7-Chloro-2′-isopropoxy-4,6-dimethoxy-6′-methylgris-2′-en-3,4′-dione (III; R = Pr^i, R′ = R″ = Me).—Alkylation of griseofulvic acid by method A with isopropyl iodide gave a mixture of 2′- and 4′-isopropyl ether which were separated by chromatography to give the *2′-isopropoxy-compound* (III; R = Pr^i, R′ = R″ = Me) (45%), m. p. 196° (from methanol) $[\alpha]_D$ +293°, $\lambda_{max.}$ 236 (ε 21,600) and 291 mμ (ε 24,000) (Found: C, 60·0; H, 5·5; Cl, 9·5; OMe, 24·6. $C_{19}H_{21}ClO_6$ requires C, 59·9; H, 5·6; Cl, 9·3; OMe, 24·5%). The corresponding *4′-isopropyl ether* (I; R = Pr^i, R′ = R″ = Me) was obtained in 33% yield and had m. p. 189° (from

TABLE 1.

Analogues (II; R′ = Me) of griseofulvic acid.

R	M. p.	$[\alpha]_D$	Formula	Found (%) C	H	N	Cl	Required (%) C	H	N	Cl	Yield (%) A	B
Pr^n	211—214°	+246°	$C_{18}H_{19}ClO_6$	58·6	5·2	—	9·7	58·9	5·2	—	9·7	—	79 [a]
Pr^i	221—224	+365 [d]	$C_{18}H_{19}ClO_6$	58·5	5·5	—	9·5	58·9	5·2	—	9·7	—	74 [a]
Bu^n	193—194	+239	$C_{19}H_{21}ClO_6$	59·9	5·6	—	9·3	59·9	5·6	—	9·3	—	81 [b]
$CH_2{:}CH{\cdot}CH_2$	200	+244	$C_{18}H_{17}ClO_6$	59·0	4·7	—	9·3	59·3	4·7	—	9·7	80 [b]	—
CH_2Ph	134 *	+199	$C_{22}H_{19}ClO_6, \frac{1}{2}EtOAc$	63·0	5·1	—	8·2	62·8	5·1	—	7·7	76 [b]	—
$C_{16}H_{33}$	122—127	+155	$C_{31}H_{45}ClO_6$	—	—	—	—	—	—	—	—	—	78 [c]
$O{\cdot}CH_2{\cdot}CO_2H$	90 *	+181	$C_{17}H_{15}ClO_8$	—	—	—	—	—	—	—	—	—	42 [c]
$Et_2N{\cdot}[CH_2]_2$ (HCl)	221—224	+207	$C_{21}H_{27}Cl_2NO_6$	54·0	6·2	2·9	14·9	53·7	6·0	3·0	15·1	28 [e]	—

A, Method A. B, Method B. * With decomp.

[a] Cryst. from acetic acid. [b] Cryst. from ethyl acetate. [c] The trione was not purified. [d] Rotation measured in $NaHCO_3$ solution. [e] Hemihydrate, cryst. from methanol–di-isopropyl ether.

TABLE 2.

Analogues (III; R = Me) of griseofulvin.

R′	R″	M. p.	$[\alpha]_D$	Formula	Found (%) C	H	N	Cl	Required (%) C	H	N	Cl	Yield (%) C	D
Et	Me	215—217°	+314°	$C_{18}H_{19}ClO_6$	58·5	5·4	—	9·4	58·9	5·2	—	9·7	17	—
Pr^n	Me	187—189	+305	$C_{19}H_{21}ClO_6$	60·1	5·8	—	9·2	59·9	5·6	—	9·3	33	—
Pr^i	Me	190—191	+310	$C_{19}H_{21}ClO_6$	59·7	5·6	—	9·6	59·9	5·6	—	9·3	28	—
Bu^n	Me	181—183	+299	$C_{20}H_{23}ClO_6$	60·8	6·1	—	9·0	60·8	5·9	—	9·0	23	—
$CH_2{:}CH{\cdot}CH_2$	Me	173	+305	$C_{19}H_{19}ClO_6$	60·2	5·0	—	9·4	60·2	5·1	—	9·4	31	—
$C_{16}H_{33}$	Me	—	+201	$C_{32}H_{47}ClO_6$	68·4	9·0	—	5·9	68·2	8·4	—	6·3	20	—
$CH_2{\cdot}CO_2Me$	Me	206—208	+271	$C_{19}H_{19}ClO_8$	55·4	4·8	—	8·5	55·6	4·7	—	8·6	27	—
CH_2Ph	Me	192—194	+260	$C_{23}H_{21}ClO_6$	64·5	5·1	—	8·2	64·4	4·9	—	8·3	18	—
Me	Et	211—213	+324	$C_{18}H_{19}ClO_6$	59·0	5·3	—	9·7	58·9	5·2	—	9·7	—	85 [f]
Me	Pr^n	186—188	+313	$C_{19}H_{21}ClO_6$	60·0	5·6	—	9·5	59·9	5·6	—	9·3	—	91
Me	Pr^i	124	+295	$C_{19}H_{21}ClO_6$	59·6	5·8	—	9·2	59·9	5·6	—	9·3	—	57 [g]
Me	Bu^n	168—169	+300	$C_{20}H_{23}ClO_6$	60·7	5·9	—	9·1	60·8	5·9	—	9·0	—	75
Me	$CH_2{:}CH{\cdot}CH_2$	202—204	+308	$C_{19}H_{19}ClO_6$	60·5	4·9	—	9·3	60·2	5·1	—	9·4	—	91
Me	CH_2Ph	244	+284	$C_{23}H_{21}ClO_6$	64·2	5·2	—	8·1	64·4	4·9	—	8·3	—	74
Me	$Me_2N{\cdot}[CH_2]_2$	160	+272	$C_{20}H_{24}ClNO_6$	56·0	6·2	3·4	8·4	56·2	6·1	3·3	8·3	—	86 [h]
Me	$Et_2N{\cdot}[CH_2]_2$	183—186	+262	$C_{22}H_{28}ClNO_6$	59·9	6·6	3·3	8·2	60·3	6·5	3·2	8·1	—	79
Me	$Me_2N{\cdot}CH_2{\cdot}CHMe$	201—202	+279	$C_{21}H_{26}ClNO_6$	59·8	6·3	3·2	8·4	59·5	6·2	3·3	8·4	—	78
Me	$Ph{\cdot}NH{\cdot}CO{\cdot}CH_2$	257—258	+277	$C_{24}H_{22}ClNO_7$	60·9	4·7	3·0	7·6	61·1	4·7	3·0	7·5	—	62
Me	$p\text{-}Cl{\cdot}C_6H_4{\cdot}NH{\cdot}CO{\cdot}CH_2$	235—236	+248	$C_{24}H_{21}Cl_2NO_7$	57·0	4·4	2·6	14·0	56·9	4·2	2·8	14·0	—	100
Me	$Ph{\cdot}CH_2{\cdot}NH{\cdot}CO{\cdot}CH_2$	183—187	+245	$C_{25}H_{24}ClNO_7$	61·6	5·2	3·0	7·4	61·8	5·0	2·9	7·3	—	70
Me	$C_4H_8N{\cdot}[CH_2]_2$	157—159	+258	$C_{22}H_{26}ClNO_6$	60·9	6·2	3·4	8·1	60·6	6·0	3·2	8·1	—	56
Me	$C_5H_{10}N{\cdot}[CH_2]_2$	187	+259	$C_{23}H_{28}ClNO_6$	59·3	6·5	2·9	7·6	59·0	6·5	3·0	7·6	—	74 [h]
Me	$^+NMe_2Et{\cdot}[CH_2]_2$ (Br^-)	196	+256	$C_{22}H_{29}BrClNO_6$	49·0	6·2	2·6	15·2	49·2	5·8	2·6	15·3	—	79 [h,i]

C, CH_2N_2 on the trione (II; R′ = Me, R = Alkyl). D, Claisen alkylation of the phenol (III; R = R′ = Me). [f] Ag_2O gave 75%. [g] Ag_2O gave 51%.

[h] Monohydrate. [i] Halogen calculated as chlorine.

TABLE 3.

Analogues (I; R = R″ = Me) of isogriseofulvin.

R′	M. p.	$[\alpha]_D$	Formula	Found (%) C	Found (%) H	Yield (%) Cl	Yield (%) A
Et	202—203°	+206°	$C_{18}H_{19}ClO_6$	58·8	5·4	9·4	25
Pr^n	162—164	+198	$C_{19}H_{21}ClO_6$	59·9	5·7	9·3	22
Pr^i	185—187	+196	$C_{19}H_{21}ClO_6$	59·9	5·6	9·5	33
Bu^n	161—164	+194	$C_{20}H_{23}ClO_6$	60·7	5·8	9·0	33
$CH_2{:}CH{\cdot}CH_2$	182—183	+199	$C_{19}H_{19}ClO_6$	60·4	5·2	9·5	24
$C_6H_5{\cdot}CH_2$	215—217	+174	$C_{23}H_{21}ClO_6$	64·5	5·2	8·0	32

A, Methylation with diazomethane.

methanol), $[\alpha]_D$ +198°, $\lambda_{max.}$ 235 (ε 19,500), 266 (ε 22,500), and 291 mμ (ε 20,400) (Found: C, 60·0; H, 5·7; Cl, 9·1; OMe, 24·8%).

6,2′-Dibutoxy-7-chloro-4-methoxy-6′-methylgris-2′-en-3,4′-dione (III; R = R′ = Bu^n, R″ = Me).—The trione (II; R = H, R′ = Me) (25·0 g.) was boiled under reflux with silver oxide (40·0 g.) and n-butyl iodide (37·5 ml.) in dry acetone (750 ml.). After 2 hr., more butyl iodide (37·5 ml.) was added and heating was continued for a further 17 hr. The solution was filtered, the combined filtrates were evaporated, and the neutral fraction was isolated with ethyl acetate. The mixture of ethers was separated by formation of the Girard-P derivative, to give the *6,2′-dibutyl ether* (III; R = R′ = Bu^n, R″ = Me) (7·8 g., 23%), m. p. 94—96° (from ether–light petroleum and then aqueous ethanol), $[\alpha]_D$ +248°, $\lambda_{max.}$ 236 (ε 23,100) and 292 mμ (ε 25,500) (Found: C, 63·0; H, 6·8; Cl, 8·3. $C_{23}H_{29}ClO_6$ requires C, 63·2; H, 6·7; Cl, 8·1%). *6,4′-Dibutoxy-7-chloro-4-methoxy-6′-methylgris-3′-en-3,2′-dione* (I; R = R′ = Bu^n, R″ = Me) (6·4 g., 19%), isolated from the fraction not forming a Girard derivative and crystallised from di-isopropyl ether, had m. p. 130—131°, $[\alpha]_D$ +180°, $\lambda_{max.}$ 235 (ε 22,300), 261 (ε 22,300), 292 (ε 22,500), and 324 mμ (ε 5600) (Found: C, 63·2; H, 6·8; Cl, 8·0%).

7-Chloro-6-hydroxy-4,2′-dimethoxy-6′-methylgris-2′-en-3,4′-dione (III; R = R″ = Me, R′ = H).—6-Benzyloxygriseofulvin (III; R = R″ = Me, R′ = CH_2Ph) (4·68 g.) was dissolved in ethyl acetate (350 ml.) and added to prereduced 5% palladised charcoal (1·0 g.) in ethyl acetate (100 ml.). The mixture was shaken with hydrogen at room temperature and pressure and after 12 min. absorption of hydrogen (1 mol.) had virtually ceased. The mixture was filtered, and the ethyl acetate solution was extracted with 0·5N-sodium hydroxide (2 × 250 ml.). Acidification of the alkaline layer gave the *phenol* (III; R = R″ = Me, R′ = H) (3·16 g., 86%), m. p. 287° (from ethyl acetate–light petroleum), $[\alpha]_D$ +338°, $\lambda_{max.}$ 235—236 (ε 21,700), 290 (ε 20,700), and 324 mμ (ε 10,000), $\nu_{max.}$ 3500 (OH), 1710 (C=O), and 1654 $cm.^{-1}$ (CO·C:C). The natural metabolite isolated by Barnes *et al.*[2] had m. p. 273—275° (decomp.; uncorr.), $\lambda_{max.}$ (in EtOH–HCl) 235·5 (ε 25,700) and 293·5 mμ (ε 27,500), and an identical infrared spectrum. The *acetate* was prepared by the action of acetic anhydride and pyridine on the phenol (it was necessary to dilute the mixture with dilute acetic acid as the acetate was readily hydrolysed by aqueous pyridine) and, crystallised from ethyl acetate, had m. p. 232—239° (decomp.), $[\alpha]_D$ +282°, $\lambda_{max.}$ 281—282 (ε 14,800), 271—274 (inflexion) (ε 13,100), and 326—328 mμ (ε 8300) (Found: C, 56·8; H, 4·7; Cl, 9·3. $C_{18}H_{17}ClO_7$ requires C, 56·8; H, 4·5; Cl, 9·3%).

5-Allyl-7-chloro-4,6,2′-trimethoxy-6′-methylgris-2′-en-3,4′-dione (VIII; R = R′ = Me, X = $CH_2{:}CH{\cdot}CH_2$).—The 4-allyl ether (III; R = R′ = Me, R″ = $CH_2{:}CH{\cdot}CH_2$) (5·0 g.) was boiled with dimethylaniline for 1 hr. under nitrogen. The cooled mixture was poured into an excess of dilute sulphuric acid and was extracted with ethyl acetate. The extract was washed thrice with water, then re-extracted with N-sodium carbonate. The combined aqueous extracts were freed from traces of ethyl acetate and acidified, precipitating the phenol (VIII; R = Me, R′ = H; X = $CH_2{:}CH{\cdot}CH_2$) (1·9 g., 38%), m. p. <100°, $[\alpha]_D$ +405° (*c* 0·64 in N-Na_2CO_3). Evaporation of the ethyl acetate solution gave starting material (1·7 g.), m. p. 200—202°. A suspension of the phenolic fraction (1·5 g.) in ether (150 ml.) was treated with an excess of ethereal diazomethane. After 30 min., the residual diazomethane was destroyed with acetic acid, and the ethereal solution was washed with N-sodium carbonate and with water. Removal of the solvent left a dark oil (1·4 g.) which was chromatographed in benzene (50 ml.) on alumina (75 g.). Elution with benzene gave *5-allylgriseofulvin* (VIII; R = R′ = Me, X = $CH_2{:}CH{\cdot}CH_2$)

(0·65 g.), m. p. 132—132·5° (from acetone–hexane), $[\alpha]_D$ +278°, $\lambda_{max.}$ 226 (ε 28,100), 274 (ε 16,100), 283 (ε 16,400), and 342 mμ (ε 4360), $\nu_{max.}$ 1710 (C=O), and 1655 cm.$^{-1}$ (CO·C:C) (Found: C, 61·2; H, 5·4; Cl, 9·1. $C_{20}H_{21}ClO_6$ requires C, 61·2; H, 5·4; Cl, 9·0%). Hydrogenation of the allyl compound (VIII; R = R′ = Me, X = CH_2:CH·CH_2) (0·35 g.) in ethyl acetate (30 ml.) in presence of 5% palladised charcoal (0·1 g.) at room temperature and pressure for 15 min. gave *7-chloro-4,6,2′-trimethoxy-6′-methyl-5-propylgris-2′-en-3,4′-dione* (VIII; R = R′ = Me, X = Pr^n) (0·22 g.), m. p. 113—114°, $[\alpha]_D$ +252°, $\lambda_{max.}$ 275—279 (infl.) (ε 16,600), 282 (ε 17,000), and 343 mμ (ε 4200), $\nu_{max.}$ 1710 (C=O) and 1660 cm.$^{-1}$ (CO·C:C) (Found: C, 61·1; H, 5·9. $C_{20}H_{23}ClO_6$ requires C, 60·9; H, 5·9%).

4-Benzyloxycarbonylmethoxy-7-chloro-6,2′-dimethoxy-6′-methylgris-2′-en-3,4′-dione (III; R = R′ = Me, R″ = CH_2·CO_2·CH_2Ph).—Treating the phenol (III; R = R′ = Me, R″ = H) with benzly bromoacetate [26] by method A gave the *ester*, m. p. 167—168° (from EtOH), $[\alpha]_D$ +233°, $\lambda_{max.}$ 236 (ε 24,500), 290 (ε 24,000), and 312—322 mμ (ε 4500) (Found: C, 61·5; H, 4·7; Cl, 7·3; OMe, 13·1. $C_{25}H_{23}ClO_8$ requires C, 61·7; H, 4·8; Cl, 7·3; OMe, 12·8%). Hydrogenation of this (4·0 g.) in ethyl acetate (200 ml.) with 5% palladised charcoal (0·8 g.) for 12 min. at room temperature gave *4-carboxymethoxy-7-chloro-6,2′-dimethoxy-6′-methylgris-2′-en-3,4′-dione* (III; R = R′ = Me, R″ = CH_2·CO_2H) (2·68 g., 82%), m. p. 240° (from AcOH), $[\alpha]_D$ +274°, $\lambda_{max.}$ 234—235 (ε 21,300), 289 (ε 20,900), and 312—323 mμ (ε 4400) (Found: C, 52·0; H, 4·8; Cl, 8·5; OMe, 15·3. $C_{18}H_{17}ClO_8$,H_2O requires C, 52·1; H, 4·6; Cl, 8·6; OMe, 15·0%). The *methyl ester*, prepared by the action of ethereal diazomethane on the acid and crystallised from acetic acid, had m. p. 267°, $[\alpha]_D$ +239° (in pyridine), $\lambda_{max.}$ 235—236 (ε 23,600), 289 (ε 23,100), and 312—322 mμ (infl.) (ε 4800) (Found: C, 55·5; H, 4·6; Cl, 8·8; OMe, 22·2. $C_{19}H_{19}ClO_8$ requires C, 55·6; H, 4·7; Cl, 8·6; OMe, 22·6%).

Formation of Amides of the Acid (III; R = R′ = Me, R″ = CH_2·CO_2H) *with the Bases* H_2N·$[CH_2]_n$·NEt_2 (*n* = 2 or 3).—*Method A*. The acid (III; R = R′ = Me, R″ = CH_2·CO_2H) (20·0 g.) in " AnalaR " dioxan (500 ml.) and pyridine (5 ml.) was treated with dicyclohexylcarbodi-imide (22·5 g.) and then, after 5 min., with redistilled 3-diethylaminopropylamine (15 ml.). After 16 hr. at room temperature dicyclohexylurea was removed by filtration, the filtrate was evaporated, and the residue shaken with 2N-hydrochloric acid (1·5 l.) and ethyl acetate (2 × 500 ml.). The mixture was filtered, the solids were washed with acid (500 ml.), and the base was liberated from the acid extracts with 40% sodium hydroxide solution. This material was extracted in ethyl acetate (3 × 500 ml.), washed with water (2 × 100 ml.), and, after removal of the solvent, chromatographed in benzene on deactivated, methanol-washed, alkaline alumina (Peter Spence; dried at 100—120°; 200 g.). Elution with ethyl acetate–benzene (1 : 9) (1 l.) gave the *3-diethylaminopropylamide* (III; R = R′ = Me, R″ = CH_2·CO·NH·$[CH_2]_3$·NEt_2) (5·2 g., 20%), m. p. 103·5—106·5° (from EtOH–Pr^i_2O), $[\alpha]_D$ +226°, $\lambda_{max.}$ 235—236 (ε 23,970), 290 (ε 22,000), and 310—326 mμ (ε 5000), $\nu_{max.}$ 3400 (NH), 1700 (C=O), 1662 (CO·C:C) and 1545 and 1662 cm.$^{-1}$ (CO·NH) (Found: C, 59·1; H, 6·6; N, 5·5; Cl, 6·9; OMe, 12·8. $C_{25}H_{33}ClN_2O_7$ requires C, 59·0; H, 6·5; N, 5·5; Cl, 7·0; OMe, 12·2%).

Method B. The acid (III; R = R′ = Me, R″ = CH_2·CO_2H) (1·0 g.) was dissolved in " AnalaR " dioxan (25 ml.), freshly distilled ethoxyacetylene (0·3 g.) in dioxan (10 ml.) was added, and the mixture kept for 24 hr. at room temperature. 3-Diethylaminopropylamine (0·75 ml.) was then added and after a further 6 hr. the solvent was removed *in vacuo*. The residue, in ethyl acetate (100 ml.), was washed successively with N-sodium carbonate (2 × 50 ml.), water (2 × 50 ml.), and 2N-hydrochloric acid (4 × 50 ml.). Acidification of the aqueous alkaline extracts gave starting material (0·31 g.). The base (III; R = R′ = Me, R″ = CH_2·CO·NH·$[CH_2]_3$·NEt_2) was liberated from the acidic extracts and isolated as previously (0·22 g., 17%); it had m. p. 95° and its infrared spectrum was identical with that of the sample prepared by method A.

Similarly the *2-diethylaminoethylamide* (III; R = R′ = Me, R″ = CH_2·CO·NH·$[CH_2]_3$·NEt_2) was obtained (13·6% by method A and 9·9% by method B), with m. p. 105—110° (solvated), $[\alpha]_D$ +217°, $\lambda_{max.}$ 234—235 (ε 25,400), 289 (ε 22,500), and 312—322 mμ (ε 5300), $\nu_{max.}$ 3400 (NH), 1710 (C=O), 1665 (CO·C:C), 1665 and 1540 cm.$^{-1}$ (CO·NH) (Found: C, 59·2; H, 7·0; N, 4·5; Cl, 6·4; OAlkyl, 17·2. $C_{24}H_{31}ClN_2O_7$,$\frac{1}{2}Pr^i_2O$ requires C, 59·4; H, 7·0; N, 5·1; Cl, 6·5; OAlkyl, 17·1%).

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[26] Clarke, *J.*, 1910, **97**, 428.