597 *Griseofulvin. Part XIII.* Homologues of Griseofulvin and 7-Chloro-4 : 6 : 4′-trimethoxy-6′-methylgris-3′-ene-3 : 2′-dione.*

By L. A. Duncanson, John Frederick Grove, and P. W. Jeffs.

The preparation is described of series of homologues of griseofulvin and of the isomer (II; R = Me).

Homologous series of enol ethers (R = alkyl) derived from griseofulvin (I; R = Me) and from the isomer, 7-chloro-4 : 6 : 4′-trimethoxy-6′-methylgris-3′-ene-3 : 2′-dione (II; R = Me), were required for an investigation of their antifungal activities. The homologues were prepared by alkylation of the trione (III) with the appropriate alcohol in the presence of toluene-*p*-sulphonic acid (method A) or with the requisite diazo-hydrocarbon (method C). Alcoholysis of griseofulvin in the presence of toluene-*p*-sulphonic acid (method B) gave essentially the same results as method A. Method C afforded mixtures of isomeric pairs of

* Part XII, *J.*, 1957, 3555.

TABLE 1. *Homologues* (I) *of griseofulvin.*[a]

R	M. p.	$[\alpha]_D^{20}$	Found (%) C	H	Cl	Formula	Required (%) C	H	Cl	Form	Solvent[b]	Yield (%)[c] Method A	B	C
Pr^n	156—157°	+271°	59·5	5·8	8·7	$C_{19}H_{21}O_6Cl$	59·9	5·6	9·3	Plates	MeOH or C_6H_6–Pet B	<1	—	19[f]
Bu^n	155	+263	60·85	5·9	—	$C_{20}H_{23}O_6Cl$	60·8	5·9	9·0	Prisms	MeOH	<1	7	42[e]
Bu^i	135—136	+264	60·75	5·8	—	$C_{20}H_{23}O_6Cl$	60·8	5·9	—	Needles	Pet A	—	25	—
n-C_5H_{11}	154	+254	61·7	6·3	—	$C_{21}H_{25}O_6Cl$	61·7	6·2	—	Prisms	MeOH	9	—	30[d]
n-C_6H_{13}	161	+248	62·5	6·2	8·6	$C_{22}H_{27}O_6Cl$	62·5	6·4	8·4	Prisms	C_6H_6–Pet	19	—	—
n-C_7H_{15}	159—160	+242	62·8	6·6	8·15	$C_{23}H_{29}O_6Cl$	63·2	6·7	8·1	Prisms	,,	7	—	—
n-C_8H_{17}	134	+237	64·1	7·0	7·9	$C_{24}H_{31}O_6Cl$	63·9	6·9	7·9	Plates	MeOH	11	—	—
										Prisms	C_6H_6–Pet			
n-$C_{10}H_{21}$	91	+217	65·0	7·6	7·4	$C_{26}H_{35}O_6Cl$	65·2	7·4	7·4	Prisms	MeOH	5	—	—
n-$C_{15}H_{31}$	89—91	+184	67·4	8·05	5·9	$C_{31}H_{45}O_6Cl$	67·8	8·3	6·45	Prisms	Et_2O–Pet or EtOH	—	—	7[d,f]

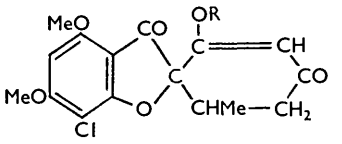
[a] $\lambda_{max.}$ 236, ~260, 292, 325—6 mμ (log ε 4·3—4·4, 4·1—4·2, 4·3—4·4, 3·7—3·8 respectively); accurate values for ε are available. For ethers (I and II; R = Et) see Grove, MacMillan, Mulholland, and Rogers, *J.*, 1952, 3979. [b] Pet = light petroleum, Pet A, b. p. 40—60°, Pet B, b. p. 60—80°. [c] 30% in Et_2O, 20% in Et_2O–Bu^nOH. [d] None of the isomer (II). [e] Calc. on trione converted. [f] in ethyl ether.

TABLE 2. *Homologues* (II).

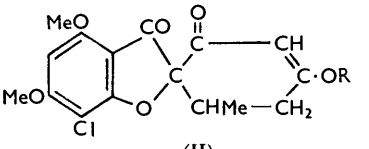
R	M. p.	$[\alpha]_D^{20}$	Found (%)[a] C	H	Cl	Form	Solvent	$\lambda_{max.}$ log ε				Yield (%)[d] Method A	B	C
Pr^n	179°	+196°	59·9	5·7	9·0	Prisms	MeOH	234	263	292	325	29	—	13[g]
								4·32	4·33	4·36	3·74			
Pr^i	188—190	+208	60·2	5·6	9·3	Needles	,,	234	265	292	325	80[e]	—	—
								4·28	4·35	4·31	3·70			
Bu^n	157—158	+192	61·1	5·8	9·0	Needles	,,	234	264	293	325	60	40	0[f]
								4·32	4·33	4·32	3·80			
Bu^i	152—155	+212	61·2	5·8	—	Prisms	,,	236	267	292	326	—	57	—
								4·31	4·36	4·32	3·75			
sec.-Bu	210—211	+210	60·75	6·2	9·0	Needles	EtOH	235	268	292	325	—	88	—
								4·28	4·37	4·32	3·73			
n-C_5H_{11}	143—144	+197	61·7	6·3	—	Needles	MeOH	235	265	292	326	66	—	0
								4·32	4·32	4·31	3·66			
n-C_6H_{13}	117—118	+195	62·5	6·5	8·3	Prisms	EtOH	234	264	292	326	62	—	—
								4·31	4·34	4·31	3·71			
cyclo-C_6H_{11}	208—210	+171	62·3	6·0[b]	—	Plates	MeOH	235	269	292	325	73[e]	—	—
								4·30	4·39	4·33	3·76			
n-C_7H_{15}	120—122	+193	63·1	6·6	7·8	Needles	EtOH	235	265	293	326	29	—	—
								4·31	4·32	4·30	3·72			
n-C_8H_{17}	129	+179	64·1	7·0	—	Needles	,,	234	265	293	326	55	—	—
								4·28	4·30	4·29	3·72			
n-$C_{10}H_{21}$	84—86	+169	65·5	7·5	7·4	Prisms	EtOH or Pet	235	265	293	326	40	—	—
								4·34	4·35	4·33	3·76			

[a] For required % see Table 1. Required: C, 62·8; H, 6·0%. [b] $C_{22}H_{25}O_6Cl$. [c] Ethanolate, m. p. 96—98°, needles from ether–ethanol (Found: C, 59·8; H, 6·4. $C_{20}H_{23}O_6Cl,C_2H_5{\cdot}OH$ requires C, 59·9; H, 6·6%). [d] Calc. on trione converted. [e] None of the isomer (I). [f] 3% in Et_2O, 20% in Et_2O–Bu^nOH. [g] in ethyl ether.

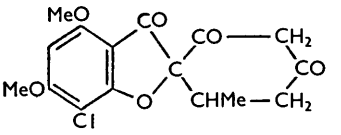
homologues of (I and II; R = Me) [1,2] which were separated by chromatography and were distinguished by their ultraviolet spectra.[2] Method A [3] yielded predominantly homologues of compound (II; R = Me), and for steric reasons this was most marked with secondary alcohols. With primary alcohols some formation of griseofulvin homologues took place but the *n*-propyl, *n*-butyl, and *n*-pentyl compounds were only obtained in good



(I)

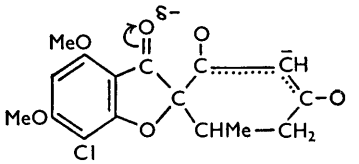


(II)

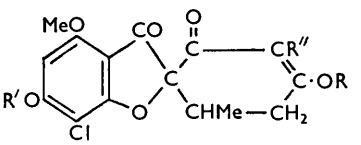


(III)

yield by method C using the diazo-hydrocarbon [4] in toluene. When the diazo-hydrocarbon was used in ether, or in ether in the presence of the alcohol, the yield of the griseofulvin homologue was lower and that of the homologue (II) progressively higher. Polarisation of the 3-carbonyl group may be a factor in determining the location of the negative charge in the mesomeric anion (IV): this polarisation will be a minimum and reaction at the 4′-position least favoured in a solvent such as toluene.



(IV)



(V)

The *n*-butyl homologues (I and II; R = Bu), prepared from (III) and diazobutane, were accompanied in low yield by the *C*-*n*-butyl derivative (V; R′ = Me, R = R″ = Bu^n). The structure was deduced from the optical rotation, which was characteristic of a compound (II) and from the ultraviolet spectrum. The latter showed a bathochromic shift of ~20 mμ, compared with (II; R = Bu^n), of the 263 mμ 1 : 3-dione enol-ether chromophore peak and caused this to overlap the coumaranone chromophore peak at 292 mμ giving a single broad band with maximum at 285 mμ. This shift is to be expected of a 3′-alkyl substituent by analogy with dimedone ethyl enol ether ($\lambda_{max.}$ 250 mμ) and the 2-methyl derivative ($\lambda_{max.}$ 268 mμ).[5] 6 : 4′-Di-*n*-butoxy-7-chloro-4-methoxy-6′-methylgris-3′-ene-3 : 2′-dione (V; R = R′ = Bu^n, R″ = H), from diazobutane and 7-chloro-6-hydroxy-4-methoxy-2′-methylgrisan-3 : 4′ : 6′-trione, had the ultraviolet spectrum characteristic of a compound (II).

Homologues (II) derived from secondary alcohols showed a small bathochromic shift and intensification of the 263 mμ band (Fig. 1 and Table 2) compared with homologues derived from normal primary alcohols: these effects were most pronounced for the *cyclo*hexyl ether. They were not observed when the spectra of the ethyl and *iso*propyl ($\lambda_{max.}$ 252 mμ) enol ethers of dimedone were compared; they are due, presumably, to steric enhancement of the interaction [6] in this series between the coumaranone and 1 : 3-dione enol ether chromophores.

[1] Oxford, Raistrick, and Simonart, *Biochem. J.*, 1939, **33**, 240.
[2] Grove, MacMillan, Mulholland, and Rogers, *J.*, 1952, 3949.
[3] Frank and Hall, *J. Amer. Chem. Soc.*, 1950, **72**, 1645.
[4] Adamson and Kenner, *J.*, 1937, 1551.
[5] Meek, Turnbull, and Wilson, *J.*, 1953, 2891.
[6] Duncanson, Grove, MacMillan, and Mulholland, *J.*, 1957, 3555.

The specific optical rotations (Fig. 2) of the homologues (I) and (II) were inversely proportional to the number of carbon atoms in R.[7]

Condensation of the trione (III) with tetra-*O*-acetyl-α-D-glucosidyl bromide [8] gave a tetra-acetylglucoside shown to have the structure (I; R = $C_6H_7O_5Ac_4$) by the ultraviolet spectrum. Attempted hydrolysis of the acetyl residues with methanolic ammonia [9] or by Zemplén's method [10] failed.

The antifungal activities of the homologues will be reported elsewhere.

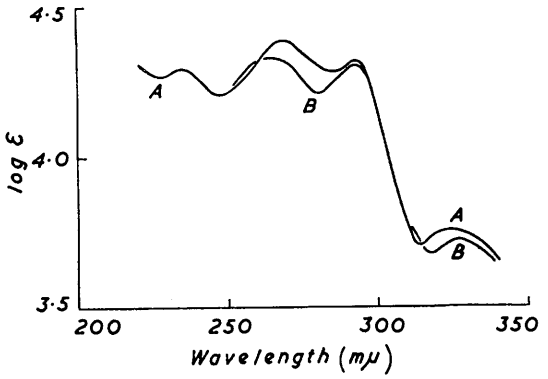


FIG. 1. *Ultraviolet absorption spectra of compounds* (II): *A*, R = cyclo*hexyl*; *B*, R = n-*hexyl*.

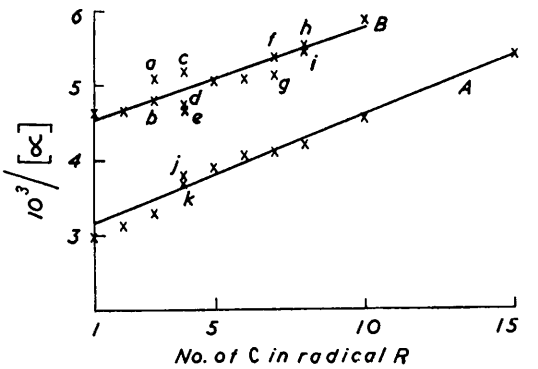


FIG. 2. *Relation of* $[\alpha]_D^{20}$ *to number of carbon atoms in the radical* R.

A, (I; R = alkyl). *B*, (II; R = alkyl).

a, Pr^n. *b*, Pr^i. *c*, Bu^n. *d*, Bu^s. *e*, Bu^t. *f*, *n*-C_7H_{15}. *g*, (V; R = R′ = Bu^n, R″ = H). *h*, *n*-C_8H_{17}. *i*, (V; R′ = Me, R = R″ = Bu^n). *j*, Bu^n. *k*, Bu^t.

EXPERIMENTAL

M. p.s are corrected. Microanalyses are by W. Brown. In chromatography B.D.H. alumina was rendered alkali-free (pH 4) and activated at 250°/15 mm. for 2 hr. Ultraviolet spectra were determined for EtOH solutions with a Unicam S.P. 500 spectrophotometer. Optical rotations were determined in acetone (*c* 1·0).

Preparation of the Enol Ethers.—(A) *Method of Frank and Hall.*[3] The trione (III) (0·5 g.), toluene-*p*-sulphonic acid (0·025 g.) and the alcohol (3 mol.) in benzene were heated under reflux in a flask fitted with a Dean and Stark separator, water being removed as formed. The reflux was arranged so that the distillate consisted chiefly of aqueous benzene; this condition was not quite fulfilled when propan-1- and -2-ol were used and small amounts of these alcohols were added from time to time. The benzene could be omitted for alcohols higher than C_5. After 6 hr. the benzene and alcohol were removed *in vacuo*. The residual gum in ether was washed with aqueous sodium hydrogen carbonate, recovered, and chromatographed (see below).

(B) *Alcoholysis of griseofulvin.* Griseofulvin (0·5 g.) and toluene-*p*-sulphonic acid (0·025 g.) were heated under partial reflux with the alcohol (25 ml.) for 12 hr. The rate of take off was 1 ml. per hr. and the volume was maintained by the addition of fresh alcohol. After removal of the alcohol *in vacuo* the residual gum was chromatographed.

[7] Gerson, *Nature*, 1957, **179**, 310.
[8] Fisher, Hawkins, and Hibbert, *J. Amer. Chem. Soc.*, 1940, **62**, 1412.
[9] Lucas, *Bull. Soc. chim. France*, 1935, **2**, 1605.
[10] Zemplén and Pacsu, *Ber.*, 1929, **62**, 1613.

(C) *Diazo-hydrocarbon method.* The trione (III) (0·35 g.), suspended in toluene (50 ml.) at 0°, was treated with an excess (*ca.* 2 mol.) of the diazo-hydrocarbon in toluene. (The diazo-hydrocarbon, prepared according to Adamson and Kenner's directions,[4] was distilled into toluene in a cold trap.) After 3 days at room temperature with frequent shaking, the toluene and excess diazo-hydrocarbon were removed *in vacuo* and the residual gum in ether was washed with sodium hydrogen carbonate solution, recovered, and chromatographed.

Diazopentadecane, prepared by the action of methanolic potassium hydroxide on methyl *N*-nitrosopentadecylcarbamate (from methyl pentadecylcarbamate [11] and nitrous fumes in ether), was used in ether without purification.

The N-*nitroso-derivative* from 1-aminopentane and synthetic (±)-pulegone formed needles, m. p. 112—113° [from light petroleum (b. p. 40—60°)] (Found: C, 67·4; H, 10·1; N, 10·9. $C_{15}H_{28}O_2N_2$ requires C, 67·1; H, 10·5; N, 10·4%). Adamson and Kenner [4] give m. p. 88·5° for the nitroso-derivative from (+)-pulegone.

Chromatography of the Crude Mixed Enol Ethers.—The gum (400 mg.) in benzene was chromatographed on alumina (30 × 1·8 cm.) in ultraviolet light, and the column was eluted consecutively with benzene–light petroleum (b. p. 60—80°) (4 : 1), benzene, benzene–ether (99 : 1, then 9 : 1), and benzene–methanol (1000 : 1, then 200 : 1). Benzene–ether (99 : 1) usually effected the complete separation on the column of two blue fluorescent bands and elution with this solvent was continued until the lower band (containing the homologue (II) had been removed. Benzene–methanol (200 : 1) brought out the upper band which contained the homologue (I). Physical constants, analytical data, and yields of the new *compounds* are given in Tables 1 and 2.

4′-n-*Butoxy*-3′-n-*butyl*-7-*chloro*-4 : 6-*dimethoxy*-6′-*methylgris*-3′-*ene*-3 : 2′-*dione* (V; R′ = Me, R = R″ = Bu^n).—Chromatography of the product from the trione (III) and diazobutane in ether or toluene revealed a third blue fluorescent band intermediate between the two principal bands. Elution with benzene–ether (9 : 1) furnished 4′-n-*butoxy*-3′-n-*butyl*-7-*chloro*-4 : 6-*dimethoxy*-6′-*methylgris*-3′-*ene*-3 : 2′-*dione* (35 mg., 7%), prisms, m. p. 214—216° (from ether or methanol), $[\alpha]_D^{20}$ +180° (Found: C, 63·8, 64·2; H, 7·0, 7·0; Cl, 7·7, 8·2. $C_{24}H_{31}O_6Cl$ requires C, 63·9; H, 6·9; Cl, 7·9%), $\lambda_{max.}$ ~234, 285, 327 mμ (log ε 4·24, 4·40, 3·77 respectively).

6 : 4′-*Di*-n-*butoxy*-7-*chloro*-4-*methoxy*-6′-*methylgris*-3′-*ene*-3 : 2′-*dione* (V; R = R′ = Bu^n, R″ = H).—7-Chloro-6-hydroxy-4-methoxy-2′-methylgrisan-3 : 4′ : 6′-trione (0·50 g.), suspended in methanol (2 ml.), was treated with excess of ethereal diazobutane. Chromatography of the product gave needles [from benzene–light petroleum (b. p. 40—60°)], m. p. 136°, of 6 : 4′-*di*-n-*butoxy*-7-*chloro*-4-*methoxy*-6′-*methylgris*-3′-*ene*-3 : 2′-*dione* (227 mg., 34%), $[\alpha]_D^{20}$ +185° (Found: C, 63·3; H, 6·7. $C_{23}H_{29}O_6Cl$ requires C, 63·2; H, 6·7%), $\lambda_{max.}$ 235, 265, 292, 325 mμ (log ε 4·33, 4·32, 4·32, 3·72 respectively).

Dimedone iso*Propyl Enol Ether.*—Dimedone (7 g.), toluene-*p*-sulphonic acid (0·2 g.) and propan-2-ol (11 g.) were heated in benzene (100 ml.) (method A) for 10 hr. The iso*propyl ether* crystallised from light petroleum (b. p. 40—60°) in prisms (2·7 g.), m. p. 47° (Found: C, 72·7; H, 9·9. $C_{11}H_{18}O_2$ requires C, 72·5; H, 10·0%), $\lambda_{max.}$ 252 mμ (ε, 18,100).

Tetra-O-*acetyl*-α-D-*glucoside of the Trione* (III) (with Dr. T. P. C. Mulholland).—Tetra-*O*-acetyl-α-D-glucosidyl bromide (4·85 g.) in acetone was added with stirring to the trione (III) (3·88 g.) in acetone (25 ml.) containing 0·93N-potassium hydroxide (12·3 ml.) at 5°. The pH was maintained at *ca.* 9 by further addition of potassium hydroxide (30 ml.) during 45 min. and the solution was kept for 4 days at room temperature, filtered and concentrated *in vacuo* at 30°. The acetone-soluble portion of the residual gum was dissolved in ether and extracted with sodium hydrogen carbonate. Unchanged trione (2·2 g.) was recovered from the acidic fraction. Slow evaporation of the dried neutral ethereal solution furnished needles (532 mg.), m. p. 122—130°. Recrystallisation from ether–methanol gave the *tetra*-O-*acetylglucoside*, needles, m. p. 128—134°, $[\alpha]_D^{17}$ +140° (*c* 1·09 in MeOH) (Found: C, 53·7; H, 5·0; Cl, 5·3. $C_{30}H_{33}O_{15}Cl$ requires C, 53·85; H, 5·0; Cl, 5·3%), $\lambda_{max.}$ ~235, ~258, 294, ~325 mμ (log ε 4·35, 4·07, 4·38, 3·77 respectively).

We thank Mr. D. Gardner and Mr. S. C. Bishop for technical assistance.

Imperial Chemical Industries Limited, Akers Research Laboratories,
The Frythe, Welwyn, Herts. [*Received, March 17th*, 1958.]

[11] Jeffreys, *Ber.*, 1897, **30**, 898.