

### 911. *Synthesis of Some Griseofulvin Analogues*

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A recent synthesis<sup>1</sup> of the racemate of griseofulvin (I; R<sup>1</sup> = Cl, R<sup>2</sup> = OMe) has been extended to the racemate of the homologue (I; R<sup>1</sup> = Cl, R<sup>2</sup> = OEt), to analogues without alkoxy groups on the aromatic ring, and to three related spirans in which the 1-oxygen atom is replaced by a sulphur or *N*-methyl group.

It has been shown<sup>1</sup> that the racemate of griseofulvin (I; R<sup>1</sup> = Cl, R<sup>2</sup> = OMe) is obtained in 5% yield by double Michael addition of methoxyethynyl prop-1-enyl ketone (IV; R = Me) to 7-chloro-4,6-dimethoxycoumaran-3-one (V) in diethylene glycol dimethyl ether-*t*-butyl alcohol, in the presence of potassium *t*-butoxide. This synthesis, as opposed to other syntheses of grisan derivatives, did not yield any of the racemate of the (*l,d*)-diastereoisomer\* (II; R<sup>1</sup> = Cl, R<sup>2</sup> = OMe).

Previous work on the correlation of structure and antifungal activity in derivatives of griseofulvin has been limited mainly to grisan derivatives containing alkoxy or hydroxyl groups on the aromatic ring. The new synthesis,<sup>1</sup> in spite of the low yield, seemed a possible route both to grise-2'-en-3,4'-diones with an alkoxy-free aromatic ring and to related spirans with the 1-oxygen atom replaced by a sulphur or nitrogen atom. This extension of the synthesis is described below.

When the present work was carried out preparative details for the prop-1-enyl ketones (IV; R = Me or Et) were not available. The procedure differed slightly from that of ref. 1*b* but the yields were similar.

Coumaranones not already available were obtained as follows. 5-Chlorocoumaranone

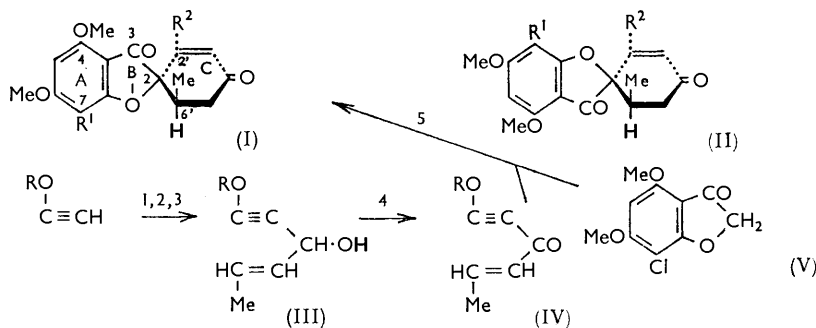
\* In an alternative system<sup>2,3</sup> of nomenclature, natural griseofulvin is referred to as (+)-griseofulvin, and the diastereoisomer (II; R<sup>1</sup> = Cl, R<sup>2</sup> = OMe) as epi-(+)-griseofulvin.

<sup>1</sup> G. Stork and M. Tomasz, *J. Amer. Chem. Soc.*, (a) 1962, **84**, 310; (b) *ibid.*, 1964, **86**, 471.

<sup>2</sup> A. Brossi, M. Baumann, M. Gerecke, and E. Kyburz, *Helv. Chim. Acta*, 1960, **43**, 1444.

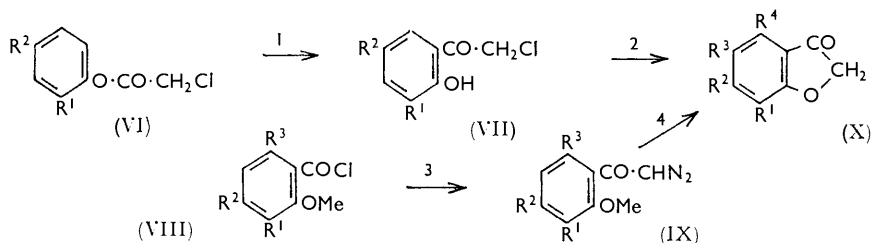
<sup>3</sup> J. F. Grove, *Quart. Rev.*, 1963, **17**, 1.

(X;  $R^3 = \text{Cl}$ ,  $R^1 = R^2 = R^4 = \text{H}$ ) was prepared from *p*-chlorophenol by way of the chloroacetate and 5-chloro-2-hydroxy- $\omega$ -chloroacetophenone (VII;  $R^1 = \text{H}$ ,  $R^2 = \text{Cl}$ ), substantially as described previously.<sup>4</sup> 7-Chloro-5-methylcoumaranone was obtained similarly, from 2-chloro-4-methylphenol. 6-Chlorocoumaranone (X;  $R^2 = \text{Cl}$ ,  $R^1 = R^3 = R^4 = \text{H}$ ) was prepared by the method<sup>5</sup> in which 4-chloro-2-methoxybenzoyl chloride



Reagents: 1, MeLi. 2, MeCH=CH·CHO. 3, H<sub>2</sub>O. 4, MnO<sub>2</sub>. 5, Bu<sup>t</sup>OK.

reacted with diazomethane and the resultant  $\omega$ -dialzo-ketone (IX;  $R^2 = \text{Cl}$ ,  $R^1 = R^3 = \text{H}$ ) was cyclised with acetic acid. 7-Chlorocoumaranone (X;  $R^1 = \text{Cl}$ ,  $R^2 = R^3 = R^4 = \text{H}$ ) was obtained in high yield from 3-chloro-2-methoxybenzoyl chloride by the latter method. A previous synthesis<sup>6</sup> of this coumaranone, from *o*-chlorophenoxyacetyl chloride with aluminium chloride, could not be repeated, and a similar synthesis of 5-chlorocoumaranone has been reported<sup>7</sup> to give trace yields. The route used above for 5-chlorocoumaranone was not applicable to 7-chlorocoumaranone since *o*-chlorophenyl chloroacetate yields<sup>8</sup> only 3-chloro-4-hydroxy- $\omega$ -chloroacetophenone with aluminium chloride. Attempted cyclisation of *o*-chlorophenoxyacetic acid with phosphorus pentoxide<sup>9</sup> or anhydrous hydrogen fluoride also failed.



Reagents: 1, AlCl<sub>3</sub>. 2, NaOAc. 3, CH<sub>2</sub>N<sub>2</sub>. 4, AcHO.

Application of Kuhn and Hensel's method to 2-chloro-6-methoxybenzoyl chloride gave only trace amounts of the required 4-chlorocoumaranone (X;  $R^1 = R^2 = R^3 = \text{H}$ ,  $R^4 = \text{Cl}$ ), m. p. 78—80°; presumably the formation of an  $\omega$ -dialzo-ketone is inhibited by steric hindrance, as in the case of mesityl chloride.<sup>10</sup>

2,3-Dihydrobenzo[*b*]thiophen-3-one was prepared by heating *o*-mercaptobenzoic acid in sulphuric acid with ethyl acetoacetate;<sup>11</sup> with acetylacetone<sup>12</sup> only the 2-acetyl derivative

<sup>4</sup> K. Fries, A. Hasselbach, and L. Schröder, *Annalen*, 1914, **405**, 346.

<sup>5</sup> R. Kuhn and H. R. Hensel, *Chem. Ber.*, 1951, **84**, 557.

<sup>6</sup> T. H. Minton and H. Stephen, *J.*, 1922, **121**, 1598.

<sup>7</sup> M. L. Kalinowski and L. W. Kalinowski, *J. Amer. Chem. Soc.*, 1948, **70**, 1970.

<sup>8</sup> H. L. Hansen, *J. Amer. Chem. Soc.*, 1937, **59**, 280.

<sup>9</sup> R. Stoermer and F. Bartsch, *Ber.*, 1900, **33**, 3175.

<sup>10</sup> W. E. Bachmann and W. S. Struve, *Org. Reactions*, 1942, **1**, 38.

<sup>11</sup> J. Craik and A. K. MacBeth, *J.*, 1925, **127**, 1637.

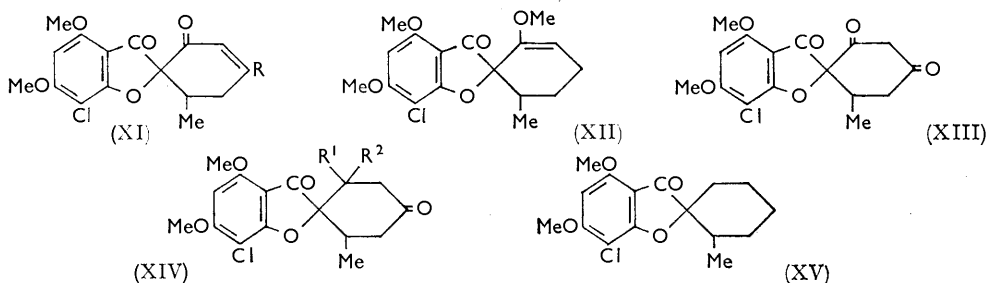
<sup>12</sup> S. Smiles and B. N. Ghosh, *J.*, 1915, **107**, 1377.

of the dihydro benzothiophenone was obtained. 7-Chloro-2,3-dihydrobenzo[*b*]thiophen-3-one was prepared as described by Dalglish and Mann.<sup>13</sup>

2,3-Dihydroindol-3-one, m. p. 84—86°, obtained by cold alkaline hydrolysis of a commercial sample of indoxyl acetate, was purified by sublimation *in vacuo*. Similar hydrolysis of 3-acetoxy-1-methylindole yielded 2,3-dihydro-1-methylindol-3-one, m. p. 37—40°.

*Stereochemistry.*—The nuclear magnetic resonance spectra of (*l,d*)- and (*d,d*)-griseofulvin and of many (*d,d*)-transformation products of griseofulvin have been reported.<sup>14-17</sup> Arison *et al.*<sup>15</sup> deduced the stereochemical configuration of the 6'-methyl groups in (*d,d*)- and (*l,d*)-griseofulvin from the band pattern between about  $\tau$  6.5 and 7.9. The difference in chemical shift between the 5' $\alpha$ - and 5' $\beta$ -protons was smaller in (*l,d*)-griseofulvin, in which they are more nearly magnetically equivalent and give rise to a 2-proton peak at  $\tau$  7.40.

This difference in the spectra of the stereoisomers was used to deduce the configurations of the new synthetic spirans. For comparison, the spectra of some pairs of griseofulvin transformation products epimeric at position 2 were examined.



The new (*l,d*)-homologues (II; R<sup>1</sup> = Cl, R<sup>2</sup> = OEt) and (XI; R = OEt), m. p. 181—183° and 200—202°, respectively, were prepared by treating the (*l,d*)-trione (XIII)<sup>18,19</sup> with ethereal diazoethane.

The difference in the multiplets at  $\tau$  7 in the spectra<sup>15</sup> of griseofulvin and its (*l,d*)-diastereoisomer was also shown in the spectra of six corresponding pairs of transformation products. The spectra of the (*l,d*)-stereoisomers (II; R<sup>1</sup> = Cl, R<sup>2</sup> = OEt and H) and (XI; R = OEt) are listed in Table 1; the spectra of the corresponding (*d,d*)-stereoisomers have been published.<sup>15,17</sup> The (*l,d*)-stereoisomers gave rise to multiplets with a comparatively narrow spread, containing the characteristic two-proton peak at  $\tau$  7.3—7.5 [7.80 in (*l,d*)-(XII)]. The peak, at  $\tau$  7.49 and 7.54, respectively, was also recognisable in the spectra of the (*l,d*)-stereoisomers (XIV; R<sup>1</sup> = H, R<sup>2</sup> = H and OMe) with a saturated ring c.

The methyl group on ring c of griseofulvin derivatives gives rise to signals at  $\tau$  9, which have been reported as doublets, though in many cases the doublets are asymmetric or separated by an intervening peak, or simulate quartets. The multiplicity may be due to an apparent coupling between the 6'-methyl group and 5'-proton resulting from the strong coupling between the 5'- and 6'-protons.

A correlation between the infrared absorption and configuration of griseofulvin derivatives has been reported.<sup>20</sup> Derivatives of griseofulvin and isogriseofulvin (XI;

<sup>13</sup> C. E. Dalglish and F. G. Mann, *J.*, 1945, 893.

<sup>14</sup> M. Gerecke, E. Kyburz, C. v. Planta, and A. Brossi, *Helv. Chim. Acta*, 1962, **45**, 2241.

<sup>15</sup> B. H. Arison, N. L. Wendler, D. Taub, R. D. Hoffsommer, C. H. Kuo, H. L. Slaters, and N. R. Trenner, *J. Amer. Chem. Soc.*, 1963, **85**, 627.

<sup>16</sup> D. Taub, C. H. Kuo, H. L. Slaters, and N. L. Wendler, *Tetrahedron*, 1963, **19**, 1.

<sup>17</sup> G. F. H. Green, J. E. Page, and S. E. Stanniforth, *J.*, 1964, 144.

<sup>18</sup> J. MacMillan, *J.*, 1959, 1823.

<sup>19</sup> A. W. Dawkins and T. P. C. Mulholland, *J.*, 1959, 1830.

<sup>20</sup> J. E. Page and S. E. Stanniforth, *J.*, 1962, 1292.

R = OMe), except 5-alkyl and 5-halogeno-derivatives, with the same configuration as (*d,d*)-griseofulvin at position 2, showed a band at about 1000 cm.<sup>-1</sup> which was replaced for (*l,d*)-griseofulvin by a band at 948 cm.<sup>-1</sup>.

TABLE 1

Compound	Proton-resonance ( $\tau$ values); $J$ (c./sec.) in parentheses						
	Aromatic H	6- and 4-Ome	2'-Subst.	3'-H	-CH-CH <sub>2</sub> -	6'-Me	Misc.
(II; R <sup>1</sup> = Cl, R <sup>2</sup> = OEt)	3.83	5.98 6.00	6.11 (q, 7) 8.79 (t, 7)	4.45	7.09— 7.65 (m) peak 7.40	9.10 (d, 6)	—
[( <i>l,d</i> )-(XI; R = OEt)]	3.92	6.03 6.06	—	4.58	6.95— 7.65 (m) peak 7.33	8.96 (d, 6.5)	6.02 (q, 7) 8.62 (t, 7) (4'-subst.)
(II; R <sup>1</sup> = Cl, R <sup>2</sup> = H) <sup>19</sup>	3.83	5.96 6.01	3.48 (d, 10)	3.76 (d, 10)	7.02— 7.58 (m) peak 7.30	8.99 (d, 6.5)	—
Racemates							
(XVI; R <sup>1</sup> = OEt, R <sup>2</sup> = R <sup>3</sup> = R <sup>4</sup> = H)	2.15— 2.48 (m) 2.64— 3.05 (m)	—	6.14 (q, 7) 8.83 (t, 7)	4.46	6.70— 7.75 (m)	9.08 (d, 6)	—
(XVI; R <sup>1</sup> = OMe, R <sup>2</sup> = R <sup>3</sup> = R <sup>4</sup> = H)	2.18— 2.49 (m) 2.72— 3.05 (m)	—	6.38	4.44	6.85— 7.75 (m)	9.09 (d, 6)	—
(XVII; R = H)	2.17— 2.83 (m)	—	6.35	4.38	6.85— 7.75 (m)	8.91 (d, 6.5)	—
(XVII; R = Cl)	2.27— 2.50 (m) 2.67— 2.95 (m)	—	6.35	4.37	6.95— 7.70 (m)	8.92 (d, 6.5)	—
(XVIII; R = Me)	2.33— 2.67 (m) 3.10— 3.44 (m)	—	6.41	4.40	6.50— 8.00 (m)	9.17 (d, 7)	7.09 ( <i>N</i> -Me)

TABLE 2

Absorption bands (900—1000 cm.<sup>-1</sup>) of (*l,d*)-spirans in bromoform solution

Compound	Absorption (cm. <sup>-1</sup> )
(II; R <sup>1</sup> = Cl, R <sup>2</sup> = OEt)	983s, 958s, 929m, 914w
(XI; R = OEt)	986m, 953m, 923w
(XIV; R <sup>1</sup> = H, R <sup>2</sup> = OMe) <sup>19</sup>	982m, 964m, 932s, 904w
(II; R <sup>1</sup> = Cl, R <sup>2</sup> = H) <sup>19</sup>	983m, 957m, 930m, 911w
(XII) <sup>19</sup>	988sh, 982m, 956m, 942m, 921m, 901m
(XIV; R <sup>1</sup> = R <sup>2</sup> = H) <sup>19</sup>	994m, 987sh, 927s, 900w
(XV) <sup>19</sup>	987m, 940s

The spectra between 900 and 1000 cm.<sup>-1</sup> of some (*l,d*)-transformation products are listed in Table 2. There was not always absorption near 948 cm.<sup>-1</sup>, but with one exception the spectra showed no band at 990—1000 cm.<sup>-1</sup>. The spectrum of (*l,d*)-(XIV; R<sup>1</sup> = R<sup>2</sup> = H) showed a band of medium strength at 994 cm.<sup>-1</sup> which is unlikely to be due to an impurity with the griseofulvin configuration since (XIV; R<sup>1</sup> = R<sup>2</sup> = H) was prepared<sup>19</sup> by way of (*l,d*)-(XIV; R<sup>1</sup> = H, R<sup>2</sup> = OMe) and (II; R<sup>1</sup> = Cl, R<sup>2</sup> = H) which do not absorb at 990—1000 cm.<sup>-1</sup>.

The synthetic gris-2'-en-3,4'-diones with the griseofulvin configuration, including 5-methyl and 5-chloro-analogues (below), absorbed at 995—1000 cm.<sup>-1</sup>, but the sulphur-containing analogues (XVII; R = Cl and H), and *N*-methyl analogue (XVIII; R = Me) did not absorb in this region.

*Synthesis of Spirans.*—As a preliminary to the preparation of new spirans, the racemate of the homologue (I; R<sup>1</sup> = Cl, R<sup>2</sup> = OEt) was prepared by Michael addition of ethoxyethynyl prop-1-enyl ketone (IV; R = Et) to 7-chloro-4,6-dimethoxycoumaran-3-one. The procedure evolved differed in detail from one later described fully.<sup>1b</sup>

Reaction in diethylene glycol dimethyl ether in the presence of 1 mol. of potassium *t*-butoxide gave about 31% of solid gris-2'-en-3,4'-diones and no starting material. No griseniones were formed when 0.2 mol. of the butoxide or 1 mol. of butyl-lithium was used as base.

The mixture of griseniones was separated by crystallisation and chromatography into the racemate, m. p. 200—202° (13%), of the (*d,d*)-homologue (I; R<sup>1</sup> = Cl, R<sup>2</sup> = OEt) of griseofulvin, an isomer C<sub>18</sub>H<sub>19</sub>ClO<sub>6</sub>, m. p. 235—237° (4%), consisting of the racemate of the (*l,d*)-homologue (II; R<sup>1</sup> = Cl, R<sup>2</sup> = OEt), and a gris-2'-en-3,4'-dione, C<sub>19</sub>H<sub>21</sub>ClO<sub>7</sub>, m. p. 208—210° (3%).

The racemate of m. p. 200—202° was identified by comparison with the (*d,d*)-stereoisomer (I; R<sup>1</sup> = Cl, R<sup>2</sup> = OEt),<sup>21</sup> m. p. 205—206°, and, as expected, was biologically active. The (*l,d*)-racemate, m. p. 235—237°, was identified by comparison with the corresponding (*l,d*)-stereoisomer (II; R<sup>1</sup> = R<sup>2</sup> = OEt), m. p. 181—183°, described above, but the racemate retained weak biological activity presumably due to residual impurity with the griseofulvin configuration. The high melting point of this racemate resembles that of racemic (*l,d*)-griseofulvin (m. p. 250—251°<sup>2</sup>), and chromatographic separation of the (*l,d*)- and (*d,d*)-racemates was difficult as with mixtures of (*l,d*)- and (*d,d*)-griseofulvin.<sup>18</sup>

The third product, C<sub>19</sub>H<sub>21</sub>ClO<sub>7</sub>, is considered to be the racemate of the (*l,d*)-homologue (II; R<sup>1</sup> = Cl, R<sup>2</sup> = OCH<sub>2</sub>·CH<sub>2</sub>·OMe) resulting from ether exchange with the solvent diethylene glycol dimethyl ether. The ultraviolet and infrared spectra (bands at 1712 and 1659 cm.<sup>-1</sup>) were similar to those for (*d,d*)- and (*l,d*)-griseofulvin, and the absence of absorption at 990—1000 cm.<sup>-1</sup> suggested that the compound was an (*l,d*)-racemate. The n.m.r. spectrum confirmed that the compound was an (*l,d*)-racemate (peak at τ 7.39). There were no peaks attributable to a 2'-ethoxyl group; instead, signals were present at τ 6.79 and 6.47, assigned to a 2'-(O·CH<sub>2</sub>·CH<sub>2</sub>·OMe) grouping. The spectrum of diethylene glycol dimethyl ether itself showed signals at τ 6.73 and 6.51.

Interaction of the appropriate aromatic methoxyl-free moiety with ethoxy- or methoxyethynyl prop-1-enyl ketone, as for 7-chloro-4,6-dimethoxycoumarone, gave the series of spirans (XVI) listed in Table 3. In contrast to the reaction between ethoxyethynyl prop-1-enyl ketone and 7-chloro-4,6-dimethoxycoumarone, only one racemic product was

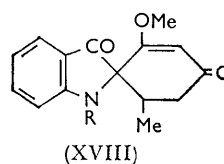
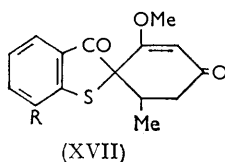
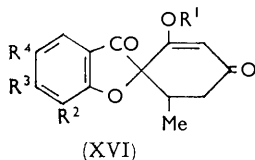
TABLE 3

Compound	Minimum concentration (p.p.m.) causing griseofulvin-like response in <i>Botrytis allii</i>
Griseofulvin (I; R <sup>1</sup> = Cl, R <sup>2</sup> = OMe) .....	0.1
Dechlorogriseofulvin (I; R <sup>1</sup> = H, R <sup>2</sup> = OMe).....	6.2 <sup>23</sup>
(I; R <sup>1</sup> = Cl, R <sup>2</sup> = OEt) .....	0.03
(II; R <sup>1</sup> = Cl, R <sup>2</sup> = OEt) .....	Inactive at 100
<b>Racemates</b>	
(I; R <sup>1</sup> = Cl, R <sup>2</sup> = OEt) .....	0.06
(II; R <sup>1</sup> = Cl, R <sup>2</sup> = OEt) .....	6.2
(II; R <sup>1</sup> = Cl, R <sup>2</sup> = O·CH <sub>2</sub> ·CH <sub>2</sub> ·OMe) .....	60.0
(XVI; R <sup>1</sup> = OEt, R <sup>2</sup> = R <sup>3</sup> = R <sup>4</sup> = H) .....	100.0
(XVI; R <sup>1</sup> = OMe, R <sup>2</sup> = R <sup>3</sup> = R <sup>4</sup> = H) .....	100.0
(XVI; R <sup>1</sup> = OEt, R <sup>2</sup> = Cl, R <sup>3</sup> = R <sup>4</sup> = H) .....	50.0
(XVI; R <sup>1</sup> = OEt, R <sup>3</sup> = Cl, R <sup>2</sup> = R <sup>4</sup> = H) .....	100.0
(XVI; R <sup>1</sup> = OEt, R <sup>2</sup> = Cl, R <sup>3</sup> = R <sup>4</sup> = H) .....	0.8
(XVI; R <sup>1</sup> = OMe, R <sup>2</sup> = Cl, R <sup>3</sup> = R <sup>4</sup> = H) .....	6.2
(XVI; R <sup>1</sup> = OEt, R <sup>2</sup> = Cl, R <sup>3</sup> = H, R <sup>4</sup> = Me) .....	1.6
(XVII; R = H) .....	25.0
(XVII; R = Cl) .....	Inactive at 100
(XVIII; R = Me) .....	Inactive at 100

obtained in each case, and this had the griseofulvin configuration. Careful chromatography of several of the products did not reveal the presence of any racemates in the (*l,d*)-series.

<sup>21</sup> J. F. Grove, J. MacMillan, T. P. C. Mulholland, and M. A. T. Rogers, *J.*, 1952, 3977.

The maximum yields of the grisendiones (XVI) were about 20% with either ethoxy- or methoxy-ethylanyl prop-1-enyl ketone, but depended on the quality of the unstable propenyl ketones, which were not prepared freshly for every experiment. The racemates showed absorption at 990—1000  $\text{cm}^{-1}$ ; the configurations were assigned on the basis of the n.m.r. spectra, in which the multiplets at about  $\tau$  7 were similar to those shown by griseofulvin and its (*d,d*) transformation products. The biological activity shown by some of the racemates is regarded as further evidence for their (*d,d*)-configurations.



On some occasions unstable crystalline by-products which did not contain the gris-2'-en-3,4'-dione system (no bands 1740—1640  $\text{cm}^{-1}$ ) were also obtained.

Michael addition of methoxyethylanyl prop-1-enyl ketone to 2,3-dihydrobenzo[*b*]thiophen-3-one and its 7-chloro-derivative gave the corresponding (*d,d*)-racemic spirans (XVII; R = H and Cl), whose configuration was shown by the n.m.r. spectra. Yields (4—10%) of the spirans were lower than those of the grisendiones.

A similar Michael addition, using 2,3-dihydro-1-methylindol-3-one as nucleophile, gave the racemic spiran (XVIII; R = Me) in higher yields (25—33%) than in the series described above. As with previous synthetic racemates, the band pattern at 6.5—8.0  $\tau$  in the n.m.r. spectrum showed that the spiran had the griseofulvin configuration. The stereoisomers due to the unsymmetrically substituted nitrogen atom are presumably too readily interconverted to be isolated.<sup>22</sup>

Attempted preparation of the spiran (XVIII; R = H) from 2,3-dihydroindol-3-one and methoxyethylanyl prop-1-enyl ketone failed.

The activities *in vitro* of the racemic spirans are listed in Table 3. The racemate of the (*l,d*)-homologue (II; R<sup>1</sup> = Cl, R<sup>2</sup> = OEt) was inactive as expected; the weak activity of the racemates of the homologues (II; R = Cl, R<sup>1</sup> = OEt or O-CH<sub>2</sub>-CH<sub>2</sub>-OMe) is presumably due to the presence of traces of impurity with the griseofulvin configuration. The (*d,d*)-homologue (I; R<sup>1</sup> = Cl, R<sup>2</sup> = OEt) showed twice the activity of the racemate. Of the racemic spirans (XVI) lacking methoxyl groups on ring A, those also lacking a chlorine substituent showed griseofulvin-like activity, but only at high concentration. Increased activity resulted from the introduction of a chlorine atom at position 7, but not at positions 5 or 6, and the 7-chloro-analogue (XVI; R<sup>1</sup> = OEt, R<sup>2</sup> = Cl, R<sup>3</sup> = R<sup>4</sup> = H) showed activity comparable with that<sup>23</sup> of (*d,d*)-dechlorogriseofulvin (I; R<sup>1</sup> = H, R<sup>2</sup> = OMe). Introduction of a 5-methyl grouping, to give (XVI; R<sup>1</sup> = OEt, R<sup>2</sup> = Cl, R<sup>3</sup> = H, R<sup>4</sup> = Me), reduced the activity. On the other hand, although the ring-A-unsubstituted sulphur-containing analogue (XVII; R = H) retained slight activity, this was destroyed by introduction of a 7-chloro-substituent; the *N*-methyl analogue (XVIII; R = Me) was also inactive.

#### EXPERIMENTAL

Melting points are corrected. Ultraviolet spectra were determined for ethanol solutions, and infrared spectra for bromoform solutions. N.m.r. spectra were obtained for deuteriochloroform solutions (tetramethylsilane as internal standard at  $\tau$  10.00) with a Varian Associates A60 spectrometer (60 Mc.). Light petroleum had b. p. 40—60°. Alumina was Woelm. Solutions were dried with sodium sulphate.

Potassium *t*-butoxide containing 1 mol. of butanol of crystallisation<sup>24</sup> was prepared freshly

<sup>22</sup> W. H. Mills, *J.*, 1943, 194.

<sup>23</sup> J. MacMillan, *J.*, 1953, 1697.

<sup>24</sup> N. A. Milas and S. M. Djokić, *Chem. and Ind.*, 1962, 405; *J. Amer. Chem. Soc.*, 1962, **84**, 3098.

for each experiment. Active manganese dioxide<sup>25</sup> was washed on the filter with hot water until the filtrate had pH 7, then dried at 120°. Dioxan and diethylene glycol dimethyl ether were purified by standard methods.

Methoxyacetylene, prepared<sup>26,27</sup> (max. yield 82%) from dimethyl chloroacetal (62 g.), had b. p. 22–23°,  $n_D^{16}$  1.3692 (lit., b. p. 22.5–24°,<sup>26</sup> 34°,<sup>1b</sup>  $n_D^{16}$  1.3697<sup>26</sup>). Some preparations ignited during quenching of the intermediate sodium salt.

1-Ethoxyhex-4-en-1-yn-3-ol (III; R = Et).—Ethoxyacetylene (27.0 g., 0.38 mol.) in ether (40 ml.) was added dropwise at 20° during 30 min. to stirred 1.54N-ethereal methyl-lithium solution<sup>28,29</sup> (227 ml., 0.35 mol.) under nitrogen. The mixture was stirred at 20° for 30 min., cooled in a bath maintained at –25° to –30° during the addition (30 min.) of redistilled crotonaldehyde (22.3 g., 0.32 mol.) in ether (100 ml.). The mixture was stirred for 1 hr. at –25°, and kept at 0° for 20 hr.

The mixture of solid and liquid was poured into ice-water (250 ml.). The organic layer and ether washings of the aqueous layer were washed with water, dried, and evaporated at <50° (bath), giving an oil. The evaporation and subsequent manipulations were carried out in ammonia-washed glass-ware. The product was fractionally distilled at 10<sup>-2</sup> mm. under nitrogen through a short Vigreux column, yielding fractions: (i) b. p. 20–65° (2.59 g.),  $n_D^{20}$  1.4732; (ii) b. p. 65–66° (25.27 g.),  $n_D^{20}$  1.4732; (iii) b. p. 65–66° (2.13 g.),  $n_D^{20}$  1.4735. Fractions (ii) and (iii) were almost pure 1-ethoxyhex-4-en-1-yn-3-ol. Fraction (i) contained impurity absorbing at ca. 1700–1740 cm<sup>-1</sup>. Yields were 51–61%. Redistillation gave the enynol as an initially colourless oil, b. p. 45–46°/10<sup>-3</sup> mm.  $n_D^{20}$  1.4738 (Found: C, 68.9; H, 8.7. Calc. for C<sub>8</sub>H<sub>12</sub>O<sub>2</sub>: C, 68.5; H, 8.6%),  $\nu_{\max}$  (film) 2267 cm<sup>-1</sup> (C≡C). No max. at 200–300 m $\mu$  in EtOH ( $\epsilon$  at 259 m $\mu$ , 298). Some impure preparations had a maximum at 259 m $\mu$ . After storage for 10 days at 0° the enynol contained much impurity (infrared spectrum) [Lit., b. p. 66.5/0.3 mm.,  $n_D^{20}$  1.4733;<sup>30</sup> b. p. 65–70° (diffusion pump)<sup>1b</sup>].

Ethoxyethynyl Prop-1-enyl Ketone (IV; R = Et).—The above alcohol (5.46 g.) was added to a mixture of manganese dioxide (55 g.) and 1,1-dichloroethane (250 ml.), previously filtered through neutral alumina (Grade I). The mixture was shaken, with cooling, for 5 min., and at room temperature for 3 hr. A total of 20.6 g. of the alcohol was oxidised batchwise and the combined products were filtered. The filtrate and washings of the cake were evaporated at 40–50° (bath) *in vacuo*. The residual oil was fractionally distilled under nitrogen at 10<sup>-2</sup> mm. through a short (10 × 0.8 cm.) and relatively unconstricted vacuum-jacketed Vigreux column, giving fractions: (i) b. p. <50°, by-products,  $n_D^{20}$  <1.4900; (ii) b. p. 50–60°,  $n_D^{20}$  1.4901–1.4918, impure product (1.45 g.),  $\nu_{\max}$  ca. 1740 cm<sup>-1</sup>; (iii) b. p. 57–60°,  $n_D^{20}$  1.4919–4922 (7.80 g., 39%), almost pure product, showing no absorption at 1700–1800 cm<sup>-1</sup>. Yields were 26–39%. Redistillation gave the propenyl ketone as an oil, b. p. 45°/10<sup>-3</sup> mm.,  $n_D^{20}$  1.4922 (Found: C, 69.3; H, 7.3. Calc. for C<sub>8</sub>H<sub>10</sub>O<sub>2</sub>: C, 69.5; H, 7.3%),  $\nu_{\max}$  (film) 2230, 1648, ~1622 cm<sup>-1</sup>; no bands 1700–1800 cm<sup>-1</sup>,  $\lambda_{\max}$  (e) 227–228 (13,800), ~250 m $\mu$  (11,180). The ketone was stored at 0° for 3 months without substantial decomposition, but older specimens gave reduced yields of grisans in the Michael reaction. [Lit.,<sup>1b</sup> b. p. 40–60° (diffusion pump),  $\nu_{\max}$  (CCl<sub>4</sub>) 2230, 1650, 1625 cm<sup>-1</sup>,  $\lambda_{\max}$  (e) 228 (11,600), 249 m $\mu$  (9100) in EtOH.]

Methoxyethynyl Prop-1-enyl Ketone (IV; R = Me).—Methoxyacetylene was converted into 1-methoxyhex-4-en-1-yn-3-ol (III; R = Me) as described above for the ethoxy-analogue, except that the methoxyacetylene was added to the reaction mixture at –5° and the salt of the alcohol was decomposed with aqueous sodium chloride solution at 0°. Fractional distillation of the product gave, after a low-boiling fraction, the required alcohol (72%), b. p. 54–55°/10<sup>-3</sup> mm.,  $n_D^{20}$  1.4775,  $\nu_{\max}$  (film) 3380, 2925, 2278, 1670 cm<sup>-1</sup> [Lit.,<sup>1b</sup> b. p. 60° (diffusion pump).]

The alcohol (26.1 g.) was oxidised with manganese dioxide as described above, with cooling for the first 5 min. Fractional distillation of the recovered product at 10<sup>-2</sup> mm. gave: (i) impure material (1.87 g.), b. p. 42–44°,  $n_D^{20}$  1.4918; (ii) fractions (7.62 g.) of the required ketone, b. p. 44–48°  $n_D^{20}$  1.4922–1.4972, containing a small amount of impurity absorbing at ca. 1770 cm<sup>-1</sup>; (iii) substantially pure ketone (3.59 g.), b. p. 48–49°,  $n_D^{20}$  1.4991,  $\nu_{\max}$  (film) 2237,

<sup>25</sup> J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, *J.*, 1952, 1094.

<sup>26</sup> H. H. Wassermann and P. S. Wharton, *J. Amer. Chem. Soc.*, 1960, **82**, 661.

<sup>27</sup> E. R. H. Jones, G. Eglinton, M. C. Whiting, and B. L. Shaw, *Org. Synth.*, Coll. Vol. IV, 1963, 404.

<sup>28</sup> C. Tegner, *Acta Chem. Scand.*, 1952, **6**, 786.

<sup>29</sup> G. Sumrell, *J. Org. Chem.*, 1954, **19**, 817.

<sup>30</sup> J. F. Arens, *Adv. Org. Chem.*, 1960, **2**, 117.

1653, 1624  $\text{cm}^{-1}$ , no absorption 1700—1800  $\text{cm}^{-1}$ ,  $\lambda_{\text{max}}$  ( $\epsilon$ ) 230 (10,600),  $\sim 255 \text{ m}\mu$  (7800). Fractions (ii) and (iii) were pure enough for use. Yields were 37—50%. [Lit.,<sup>1b</sup> b. p. 65—80° (diffusion pump).]

*Coumaran-3-one*.—This had m. p. 101—102°,  $\lambda_{\text{max}}$  ( $\log \epsilon$ )  $\sim 247$  (3.93), 249 (3.95), 325  $\text{m}\mu$  (3.69).

*7-Chloro-4,6-dimethoxycoumaran-3-one*.<sup>1b,31</sup>—This had m. p. ca. 220° (decomp.),  $\lambda_{\text{max}}$  ( $\log \epsilon$ ) 236 (4.38), 286 (4.42), 320  $\text{m}\mu$  (3.81).

*5-Chlorocoumaran-3-one*.—A mixture of *p*-chlorophenol (98 g.) and chloroacetyl chloride (125 g.) was refluxed until the temperature of the liquid reached 140°, and kept at 135—140° for 5 hr. Distillation of the product gave the  $\omega$ -chloroacetate (145 g.), b. p. 162—163°/15 mm.

The chloroacetate (144 g.) was treated with powdered aluminium chloride (150 g., 1.5 mol., instead of ca. 4 mol. as used by Fries *et al.*<sup>4</sup>) in portions during 10 min., and the mixture was then heated rapidly to 140° (bath). When the vigorous reaction had moderated, the mixture was heated for 5 hr. at 140—150°, cooled, treated with ice and then with 5*N*-hydrochloric acid, heated at 100° for 15 min., and allowed to cool. Most of the supernatant aqueous layer was decanted and the residue was steam-distilled. The product (64 g.), obtained by filtration of the distillate and extraction of the filtrate with ethyl acetate, was boiled with crystalline sodium acetate (17 g.) in ethanol (300 ml.) for 30 min., and the cooled solution was poured into water (1 l.). The resulting precipitate was crystallised once from ethanol, giving yellow plates (38 g.), m. p. 114—117°, which were sublimed *in vacuo* (bath 110—120°,  $10^{-1}$  mm.), giving 5-chlorocoumaran-3-one as plates, m. p. 118° (Found: C, 57.3; H, 3.1; Cl, 20.9. Calc. for  $\text{C}_9\text{H}_5\text{ClO}_2$ : C, 57.0; H, 3.0; Cl, 21.0),  $\lambda_{\text{max}}$  ( $\log \epsilon$ )  $\sim 234$  (3.81), 243 (3.81), 248 (3.81), 340  $\text{m}\mu$  (3.64). (Lit., m. p. 117°,<sup>4</sup> 113.5°.<sup>6</sup>)

The benzylidene derivative formed yellow needles from ethanol, m. p. 169—170° (Found: C, 70.35; H, 3.5; Cl, 13.9. Calc. for  $\text{C}_{15}\text{H}_9\text{ClO}_2$ : C, 70.1; H, 3.5; Cl, 13.8). (Lit., m. p. 169°,<sup>4</sup> 165°.<sup>6</sup>)

The semicarbazone formed colourless needles from acetone, m. p. 241—243° (decomp.) (Found: C, 48.1; H, 3.9; N, 18.7. Calc. for  $\text{C}_9\text{H}_8\text{ClN}_3\text{O}_2$ : C, 47.9; H, 3.55; N, 18.6). (Lit.,<sup>6</sup> m. p. 221°.)

*7-Chloro-5-methylcoumaran-3-one*.—2-Chloro-4-methylphenol (10.8 g.) reacted with chloroacetyl chloride (13 g.) as described above for *p*-chlorophenol, giving the  $\omega$ -chloroacetyl derivative (11.7 g.) as an oil, b. p. 72—82°/30 mm. (Found: Cl, 33.6.  $\text{C}_9\text{H}_8\text{Cl}_2\text{O}_2$  requires Cl, 32.4%).

The derivative (12.5 g.) was treated with aluminium chloride (11.5 g.), the mixture was heated at 140° for 5 hr., then worked up as described in the preceding experiment. The crude dry steam-volatile product (7.26 g.) was boiled in ethanol (35 ml.) with crystalline sodium acetate (2.0 g.) for 30 min., and the mixture was poured into water. The product which separated was crystallised from ethanol giving: (i) 2.4 g., m. p. 112—114°; (ii) impure solid products; (iii) gums.

Fractions (i) and (ii) sublimed *in vacuo* at  $10^{-1}$  mm., giving the *coumaranone* (2.37 g.), plates (from ethanol), m. p. 115—116° (Found: C, 58.9; H, 3.9; Cl, 19.0.  $\text{C}_9\text{H}_7\text{ClO}_2$  requires C, 59.2; H, 3.9; Cl, 19.4),  $\lambda_{\text{max}}$  ( $\log \epsilon$ )  $\sim 252$  (3.92), 258 (3.96), 339  $\text{m}\mu$  (3.74).

The *benzylidene derivative* crystallised from ethanol in yellow needles, m. p. 176—177° (Found: C, 71.3; H, 4.3; Cl, 13.3.  $\text{C}_{16}\text{H}_{11}\text{ClO}_2$  requires C, 71.0; H, 4.1; Cl, 13.1%).

The *semicarbazone* formed prisms (from acetone), m. p. 239—242° (decomp.) (Found: C, 49.8; H, 4.3; Cl, 15.0; N, 17.1.  $\text{C}_{10}\text{H}_{10}\text{ClN}_3\text{O}_2$  requires C, 50.1; H, 4.2; Cl, 14.8; N, 17.5%).

*6-Chlorocoumaran-3-one*.—6-Chlorocoumaranone was obtained from 4-chloro-2-methoxybenzoic acid as described by Kuhn and Hensel<sup>5</sup> except that the intermediate  $\omega$ -diazo-ketone was not purified.

4-Chloro-2-methoxybenzoic acid<sup>5</sup> (2.57 g.) was converted into the acid chloride, which with ethereal diazomethane gave the yellow  $\omega$ -diazo-ketone (IX;  $\text{R}^2 = \text{Cl}$ ,  $\text{R}^1 = \text{R}^3 = \text{H}$ ) as an oil which solidified. The crude diazo-ketone and glacial acetic acid (6 ml.) were heated together at 60° until gas evolution ceased (5 min.). The yellow crystals (1.71 g., m. p. 123—124°) obtained by cooling and concentration of the solution were sublimed at 100—110°/ $10^{-2}$  mm., then crystallised from light petroleum (b. p. 80—100°), giving needles (1.29 g.) of 6-chlorocoumaran-3-one, m. p. 126—127° (Found: C, 57.0; H, 3.0; Cl, 20.35. Calc. for  $\text{C}_8\text{H}_5\text{ClO}_2$ : C, 57.0; H, 3.0; Cl, 21.0%),  $\lambda_{\text{max}}$  ( $\log \epsilon$ )  $\sim 252$  (4.10),  $\sim 256$  (4.12), 323  $\text{m}\mu$  (3.82). (Lit.,<sup>5</sup> m. p. 123—123.5°.)

<sup>31</sup> J. MacMillan, T. P. C. Mulholland, A. W. Dawkins, and G. Ward, *J.*, 1954, 429.



The semicarbazone formed prisms, m. p. 228—230° (decomp.) (from acetone) (Found: C, 47.65; H, 3.6; Cl, 15.5; N, 18.2. Calc. for  $C_9H_8ClN_3O_2$ : C, 47.9; H, 3.55; Cl, 15.7; N, 18.6%). [Lit.,<sup>5</sup> m. p. 220° (decomp.)]

The *benzylidene derivative* crystallised from ethanol in yellow needles, m. p. 161—162° (Found: C, 69.9; H, 3.6; Cl, 13.6.  $C_{15}H_9ClO_2$  requires C, 70.1; H, 3.5; Cl, 13.8%).

**3-Chloro-2-methoxytoluene.**—A solution of commercial 2-chloro-6-methylphenol (25.0 g.) in water (90 ml.) containing sodium hydroxide (7.66 g.) was stirred at 10° during dropwise addition of dimethyl sulphate (17.4 ml.) during 10 min. When the addition was complete the mixture was kept at room temperature for 30 min., boiled for 30 min., cooled, and the oily product (23.8 g.) recovered by ether extraction. The product was a mixture of the required methyl ether with 5-chloro-2-methoxytoluene derived from impurity in the starting material. Fractional distillation of the mixture (172 g.) from several experiments, at 20 mm., gave fractions (yield, and  $n_D^{20}$  in parentheses): (i) b. p. 82—84° (12.9 g., 1.5228); (ii) b. p. 84—86° (83.8 g., 1.5248); (iii) b. p. 86—88° (15.2 g., 1.5262); (iv) b. p. 86—88° (6.0 g., 1.5267); (v) b. p. 88—90° (4.5 g., 1.5288); (vi) b. p. 90—93° (9.8 g.), m. p. 37°.

Fraction (ii) consisted of the required *3-chloro-2-methoxytoluene* (Found: C, 61.6; H, 5.75; Cl, 22.5; OMe, 20.0.  $C_8H_7ClO$  requires C, 61.4; H, 5.8; Cl, 22.6; OMe, 19.8%).

Fraction (vi) crystallised from ethanol in plates, m. p. 37°, of the isomeric 5-chloro-2-methoxytoluene (Found: C, 60.4; H, 5.7; Cl, 22.4%). (Lit.,<sup>32</sup> b. p. 212.6—214.6°/758 mm.). The structure of this by-product was established by oxidation of the compound (700 mg.) with potassium permanganate as described for the 3-chloro-analogue (below). Recovery of the product gave starting material (246 mg.), and 5-chloro-2-methoxybenzoic acid (187 mg.) as needles, m. p. 85—87°, which, on recrystallisation from benzene—light petroleum (b. p. 60—80°), yielded a dimorphic form (infrared spectrum) as needles, m. p. 100—101° (Found: C, 51.8; H, 3.7; Cl, 19.2. Calc. for  $C_8H_7ClO_3$ : C, 51.5; H, 3.8; Cl, 18.5%). The low-melting form was obtained in two experiments but could not be obtained by recrystallising the high-melting form. (Lit.,<sup>32</sup> m. p. 81—82°.)

An authentic specimen of 5-chloro-2-methoxybenzoic acid was prepared from 5-chloro-2-hydroxybenzoic acid by methylation with dimethyl sulphate followed by alkaline hydrolysis of the resulting methyl ester methyl ether (cf. ref. 5). The product formed needles, m. p. 101—102° (from ethanol), identical (mixed m. p. and infrared spectrum) with the above acid, m. p. 100—101°.

**3-Chloro-2-methoxybenzoic Acid.**—A stirred refluxing mixture of 3-chloro-2-methoxytoluene (10.0 g.) and water (200 ml.) was treated with potassium permanganate (30 g.), added in eight portions at intervals of 30 min. When addition was complete the mixture was boiled for 2 hr. (no excess permanganate present), cooled, and filtered. The cake was washed with water and with ether, and the aqueous filtrates with ether. Recovery from the ethereal fractions gave starting material (2.35 g.). On acidification of the aqueous fraction with concentrated hydrochloric acid 3-chloro-2-methoxybenzoic acid separated as prisms (5.50 g.), m. p. 121—123°. Recrystallisation from ethanol gave prisms, m. p. 122—123° (Found: C, 51.7; H, 3.9; Cl, 19.2. Calc. for  $C_8H_7ClO_3$ : C, 51.5; H, 3.8; Cl, 19.0%). (Lit.,<sup>33</sup> m. p. 120—121°.)

**7-Chlorocoumaran-3-one.**—The above acid (2.63 g.) was converted into the coumaranone by way of the corresponding acid chloride and  $\omega$ -diazo-ketone as for 6-chlorocoumaranone. The crude solid product (from acetic acid) was sublimed *in vacuo*, then crystallised from light petroleum (b. p. 80—100°), giving the coumaranone (1.43 g.) as plates, m. p. 113—114° (Found: C, 57.3; H, 3.0; Cl, 20.85. Calc. for  $C_8H_5ClO_2$ : C, 57.0; H, 3.0; Cl, 21.0%),  $\lambda_{max}$  (log  $\epsilon$ ) 250 (3.90), 256 (3.93), 327  $m\mu$  (3.73). (Lit.,<sup>6</sup> m. p. 110.5°.)

The semicarbazone formed prisms, m. p. 243—245° (decomp.) (from acetone) (Found: C, 47.3; H, 3.5; Cl, 15.5; N, 18.25. Calc. for  $C_9H_8ClN_3O_2$ : C, 47.9; H, 3.55; Cl, 15.7; N, 18.6%). (Lit.,<sup>6</sup> m. p. 228°.)

The *benzylidene derivative* crystallised from ethanol in yellow needles, m. p. 146—147° (Found: C, 70.0; H, 3.4; Cl, 15.2.  $C_{15}H_9ClO_2$  requires C, 70.1; H, 3.5; Cl, 13.8%).

Attempted cyclisation of *o*-chlorophenoxyacetic acid with phosphorus pentoxide in benzene at the b. p.,<sup>9</sup> or with anhydrous hydrogen fluoride at room temperature gave no 7-chlorocoumaranone. Attempts to obtain the coumaranone by the method of Minton and Stephen<sup>6</sup> (yield not stated) also failed to yield any pure product.

<sup>32</sup> A. Peratoner and G. B. Condorelli, *Gazzetta*, 1898, **28**, I, 197.

<sup>33</sup> N. W. Hirwe, K. N. Rana, and K. D. Gavankar, *Proc. Indian Acad. Sci.*, 1938, **8**, 208.

**3-Chloro-2-methylphenol.**—3-Chloro-2-methylaniline (5.0 g.) was diazotised, and the resulting solution heated on a steam-bath, as described by Noelting.<sup>34</sup> On cooling, the phenol separated as light yellow needles (3.9 g.), m. p. 85—87°. Recrystallisation from water (charcoal) gave needles, m. p. 87—88° (Found: C, 59.0; H, 5.1; Cl, 24.8. Calc. for C<sub>7</sub>H<sub>7</sub>ClO: C, 59.0; H, 4.95; Cl, 24.9%). (Lit.,<sup>34,35</sup> m. p. 86°.)

**2-Chloro-6-methoxytoluene.**—The above phenol (75.0 g.) was methylated with dimethyl sulphate, yielding the methyl ether as an oil (74.9 g.), b. p. 85°/12 mm.,  $n_D^{20}$  1.5390 (Found: C, 61.6; H, 6.0; Cl, 23.0; OMe, 19.0. Calc. for C<sub>8</sub>H<sub>9</sub>ClO: C, 61.4; H, 5.8; Cl, 22.6; OMe, 19.8%). (Lit.,<sup>35</sup> b. p. 213.5°.)

**2-Chloro-6-methoxybenzoic Acid.**—A mixture of the above ether (15.0 g.), potassium permanganate (30.0 g.), and water (400 ml.) was heated under reflux with vigorous stirring until no excess of permanganate remained (3 hr.). The cooled mixture was filtered and the cake was washed with water and with ether. Starting material (5.2 g.) was recovered from the filtrates by extraction with ether.

The aqueous fraction was acidified with concentrated hydrochloric acid, giving the product (5.40 g.), m. p. 144—145°, as prisms. More product (1.21 g.), m. p. 143—145°, was recovered from the mother-liquor by extraction with ethyl acetate. A specimen crystallised from ethyl acetate–light petroleum or benzene–light petroleum had m. p. 144—145° (prisms) (Found: C, 51.5; H, 3.8; Cl, 19.1. Calc. for C<sub>8</sub>H<sub>7</sub>ClO<sub>3</sub>: C, 51.5; H, 3.8; Cl, 19.0%). (Lit.,<sup>35</sup> m. p. 141°.)

**4-Chlorocoumaran-3-one.**—2-Chloro-6-methoxybenzoic acid (3.50 g.) was converted into the acid chloride with thionyl chloride in the usual way.<sup>5</sup> The product in ether (40 ml.) was kept with ethereal diazomethane (from 7.8 g. of nitrosomethylurea) for 20 hr. at 0°. The mixture was evaporated (large excess of unreacted CH<sub>2</sub>N<sub>2</sub>) and the residual gum was heated with acetic acid (8 ml.) at 60° for 5 min. The solution was evaporated and the residue was crystallised from benzene–light petroleum, giving starting material (1.68 g.) and a gum (1.7 g.).

The gum, in ether, was washed with sodium hydrogen carbonate solution. The neutral fraction recovered from the ether was extracted with boiling light petroleum (b. p. 80—100°) and the gum obtained from the extract crystallised from ether–light petroleum, giving a nitrogenous by-product (94 mg.), m. p. mainly *ca.* 170°, which gave little colour with concentrated sulphuric acid. The gum from the mother liquor (strong red colour with sulphuric acid) was sublimed at 120°(bath)/10<sup>-2</sup> mm. and the sublimate (0.2 g.) resublimed. The semi-solid sublimate was freed from most of the oily material by pressing on a porous tile, then crystallised three times from ether–light petroleum, giving plates (9 mg.), m. p. 78—80°, of 4-chlorocoumaranone (Found: C, 57.2; H, 3.1. C<sub>8</sub>H<sub>6</sub>ClO<sub>2</sub> requires C, 57.0; H, 3.0%),  $\nu_{\max}$  (Nujol) 1715, 1613, 1590 cm.<sup>-1</sup>,  $\lambda_{\max}$  (log  $\epsilon$ ) 252 (3.92), 259 (3.92), 326 m $\mu$  (3.72). The compound gave a red colour with concentrated sulphuric acid and reduced Fehling's solution on warming.

**2,3-Dihydrobenzo[b]thiophen-3-one.**—This was obtained (40%) by heating *o*-mercaptobenzoic acid with ethyl acetoacetate in concentrated sulphuric acid,<sup>11</sup> and had m. p. 67—69° (Found: C, 63.8; H, 4.1. Calc. for C<sub>8</sub>H<sub>8</sub>O<sub>2</sub>S: C, 64.0; H, 4.0%),  $\nu_{\max}$  (Nujol) 1706, 1600, 1572 cm.<sup>-1</sup>,  $\lambda_{\max}$  (log  $\epsilon$ ) ~231 (4.40), 236 (4.46), 258 (3.74), ~263 (3.64), ~305 m $\mu$  (3.18). (Lit.,<sup>36</sup> m. p. 71°.)

Attempted preparation of the compound using acetylacetone instead of ethyl acetoacetate, as described by Smiles and Ghosh,<sup>12</sup> gave only 2-acetyl-3-hydroxybenzo[b]thiophen (79%), m. p. 81° (Found: C, 62.6; H, 4.3. Calc. for C<sub>10</sub>H<sub>8</sub>O<sub>2</sub>S: C, 62.45; H, 4.2%),  $\nu_{\max}$  (Nujol) 1623, 1600sh, 1568 cm.<sup>-1</sup>,  $\lambda_{\max}$  (log  $\epsilon$ ) 210 (4.30), ~257 (4.22), 265 (4.27), ~298 (4.10), 306 m $\mu$  (4.17). (Lit.,<sup>37</sup> m. p. 79°.)

7-Chloro-2,3-dihydrobenzo[b]thiophen-3-one,<sup>13</sup> purified by sublimation *in vacuo* and crystallisation from light petroleum (b. p. 60—80°), had m. p. 105—108° (Found: C, 52.2; H, 2.8. Calc. for C<sub>8</sub>H<sub>5</sub>ClOS: C, 52.1; H, 2.7%),  $\nu_{\max}$  (Nujol) 1691br, 1582 cm.<sup>-1</sup>,  $\lambda_{\max}$  (log  $\epsilon$ ) 239 (4.30), 300 (3.59), 310 m $\mu$  (3.70). (Lit.,<sup>13</sup> m. p. 103—106°.)

**2,3-Dihydroindol-3-one.**—A powdered commercial sample of indoxyl acetate, m. p. 133° (3.00 g.), was stirred under nitrogen with methanol (3 ml.) and 20% aqueous potassium hydroxide (15 ml.) for 3.5 hr. at room temperature. The solution was diluted with water (20 ml.), cooled

<sup>34</sup> E. Noelting, *Ber.*, 1904, **38**, 1015.

<sup>35</sup> F. Ullmann and P. L. Panchaud, *Annalen*, 1906, **350**, 108.

<sup>36</sup> P. Friedländer, *Ber.*, 1906, **39**, 1060.

<sup>37</sup> A. W. H. Barton and E. W. McClelland, *J.*, 1947, 1574.

to 0°, and saturated with carbon dioxide. The product, recovered from the mixture by ether extraction under nitrogen cover, sublimed at 105°/10<sup>-3</sup> mm., giving 2,3-dihydroindol-3-one (1.17 g.) as a yellow solid, m. p. 84—86° (rapid heating), which soon discoloured in air,  $\nu_{\max}$  (Nujol) 3384, 1710sh, 1690br, 1620, 1583sh cm<sup>-1</sup>. (Lit.,<sup>38</sup> m. p. 85°.)

**2,3-Dihydro-1-methylindol-3-one.**—*N*-Methyl-*o*-carboxyphenylglycine<sup>39</sup> (9.45 g.) was heated under reflux with anhydrous sodium acetate (7.5 g.) and acetic anhydride (150 ml.) for 3 hr. The mixture was evaporated *in vacuo* and the residue was extracted with methanol. The extract was concentrated and diluted with water, giving 3-acetoxy-1-methylindole (5.50 g.), m. p. 57°, as a green solid which was decolourised by recrystallisation from light petroleum (charcoal), yielding prisms m. p. 59° (Found: C, 69.9; H, 5.95; N, 7.3. Calc. for C<sub>11</sub>H<sub>11</sub>NO<sub>2</sub>: C, 69.8; H, 5.9; N, 7.4%),  $\nu_{\max}$  (Nujol) 1741, 1614 cm<sup>-1</sup>,  $\lambda_{\max}$  (log  $\epsilon$ ) 223 (4.54), 288 m $\mu$  (3.76). (Lit.,<sup>39</sup> m. p. 57°.)

Hydrolysis of the above acetate (3.00 g.) as described above gave a gum (2.18 g.) which was sublimed at 80°/10<sup>-3</sup> mm., yielding 2,3-dihydro-1-methylindol-3-one as a yellow crystalline solid (1.34 g.), m. p. 37—40° (Found: C, 73.4; H, 6.1. C<sub>9</sub>H<sub>9</sub>NO requires C, 73.45; H, 6.2%),  $\nu_{\max}$  (Nujol) ~3200br, 1665, 1613, 1582 cm<sup>-1</sup>. The compound crystallised from ether (under nitrogen) in yellow prisms but the m. p. fell to 35—40°.

**Racemic Spirans.**—(a) *From ethoxyethynyl prop-1-enyl ketone.* (1) 7-Chloro-2'-ethoxy-4,6-dimethoxy-6'-methylgris-2'-en-3,4'-dione. Potassium *t*-butoxide [1.0 mol. prepared from potassium (193 mg.) as described above] was shaken in nitrogen with diethylene glycol dimethyl ether (*ca.* 15 ml.), and the turbid solution was added quickly to a solution of 7-chloro-4,6-dimethoxy-coumaranone (1.11 g., 1.0 mol.) and ethoxyethynyl prop-1-enyl ketone (0.81 g., 1.2 mol.) in the same solvent (100 ml.) at 30°. The mixture became red and the temperature rose to 34°. After storage at room temperature for 20 hr. the mixture was treated with acetic acid (10 ml.) and evaporated *in vacuo*. The residue was extracted with boiling ethyl acetate and the material recovered from the extract was extracted with boiling benzene. The benzene extract was concentrated and chromatographed on alumina (15 × 2.0 cm.; Grade II, acid) (Column A). Elution with benzene and benzene-methanol (100 : 1 to 5 : 1) gave a semi-solid product (1.57 g.) which was rechromatographed on alumina (22 × 3.0 cm.) (Column B). Elution gave the following fractions (colours viewed in ultraviolet light): (i) (200 : 1, 100 ml.), forerun; (ii) (125 ml.) a yellow band giving 574 mg. on recovery; (iii) (25 ml.) blue and violet bands (71 mg.); (iv) (75 ml.) a second blue band (113 mg.).

Fraction (ii) with ethanol gave a solid (186 mg.) which was crystallised four times from ethyl acetate yielding the *racemate* of (*d,d*)-7-chloro-2'-ethoxy-4,6-dimethoxy-6'-methylgris-2'-en-3,4'-dione (I; R<sup>1</sup> = Cl, R<sup>2</sup> = OEt) as solvated prisms which evolved gas at 100—110° without melting, and melted at 200—202°. Drying at 100° *in vacuo* gave solvent-free opaque prisms (139 mg.), m. p. 200—202° (Found: C, 59.3, 59.2; H, 5.3, 5.3; Cl, 9.5. C<sub>18</sub>H<sub>19</sub>ClO<sub>6</sub> requires C, 58.8; H, 5.2; Cl, 9.7%),  $\nu_{\max}$  ~1707, 1657, 1653, 994s, 932w cm<sup>-1</sup>, identical with the spectrum of the (*d,d*)-stereoisomer<sup>21</sup> in bromoform,  $\nu_{\max}$  (Nujol) 1699, 1652, cm<sup>-1</sup>, distinct from the spectrum of the (*d,d*)-stereoisomer in Nujol. The ultraviolet spectrum [ $\lambda_{\max}$  (log  $\epsilon$ ) 236 (4.35), ~253 (4.21), 291—292 (4.39), ~322 m $\mu$  (3.74)] and n.m.r. spectrum were identical with the corresponding spectra of the (*d,d*)-stereoisomer. Total yield of the *racemate* was 13% (see below).

The crystallisation mother-liquors and fractions (iii)—(iv) from column B were separated by treatment with ether and ethyl acetate into gums and solid fractions (432 mg.) which consisted of a mixture of gris-2'-en-3,4'-diones (strong absorption *ca.* 1710 and 1660 cm<sup>-1</sup>) with a wide range in m. p. The solid product was chromatographed on alumina (36 × 2.0 cm.; acid, II) (Column C). After a fore-run containing yellow and white fluorescent bands (giving 12 mg. on recovery) had been eluted with benzene (8 l.), further elution with benzene-methanol (500 : 1) gave fractions: (i) (800 ml.) no colour, yielding 6 mg.; (ii) (750 ml.) a violet fluorescing band yielding 291 mg. on recovery; (iii) (500 ml.) no fluorescence, giving 7 mg.; (iv) (3 l.) a second violet band giving 82 mg.

Fraction (ii) consisted of a mixture of the above *racemate* and an isomeric *racemate*, which was separated by further chromatography (see below).

Fraction (iv), m. p. 199—201° was washed with ether, then crystallised from ethyl acetate-light petroleum, giving prisms (58 mg., 3%), m. p. 208—210°, of the *racemate* of (*l,d*)-7-chloro-2'-( $\omega$ -methoxyethoxy)-4,6-dimethoxy-6'-methylgris-2'-en-3,4'-dione (II; R<sup>1</sup> = Cl, R<sup>2</sup> =

<sup>38</sup> D. Vorländer and B. Drescher, *Ber.*, 1902, **35**, 1701.

<sup>39</sup> L. Ettinger and P. Friedländer, *Ber.*, 1912, **45**, 2075.

O-CH<sub>2</sub>-CH<sub>2</sub>-OMe) (Found: C, 57.8, 57.35; H, 5.45, 5.3; Cl, 8.5. C<sub>19</sub>H<sub>21</sub>ClO<sub>7</sub> requires C, 57.5; H, 5.3; Cl, 8.9%),  $\nu_{\max}$  ~1712, 1659, 1652, 980m, 957m, 927w cm.<sup>-1</sup>,  $\lambda_{\max}$  (log  $\epsilon$ ) 236 (4.43), ~253 (4.23), 289 (4.36), 320 m $\mu$  (2.76),  $\tau$  3.86, 4.41, 5.97, 6.00, 6.47 (t, 5) and 6.79 (O-CH<sub>2</sub>-CH<sub>2</sub>-OMe), peak, 7.39, (5'-protons) in a multiplet 7.15—7.63, 9.09 (d, 6).

Part (247 mg.) of fraction (ii) from Column C was chromatographed on alumina (37  $\times$  2.0 cm. neutral, grade II) (Column D) in benzene. Elution with benzene-methanol (1000 : 1) gave only a single blue fluorescent band. The first fractions of the band gave mixtures of the racemates of the homologues (II and I; R<sup>1</sup> = Cl, R<sup>2</sup> = OEt), and the last-eluted fractions yielded the latter racemate in pure form (34 mg.), m. p. 200—202°.

Material from the mother liquors and mixed fractions from Column D were chromatographed in benzene on alumina (38  $\times$  2.0 cm., neutral, III). Elution of the column with benzene caused the blue fluorescing band to separate into lower deeper and upper paler blue portions but the zones were not completely resolved. After a fore-run (4.7 l.), elution of the fluorescent band gave: (i) (1.5 l.) lower deep blue zone collected in 15 fractions, all giving solids (total 80 mg.), m. p. 235—237°; (ii) (750 ml.) mixed zone giving 38 mg.; (iii) (1.7 l.) and benzene-methanol (1000 : 1) (2 l.), paler blue zone yielding a gum (79 mg.) which solidified on trituration with ethyl acetate.

Fraction (iii) crystallised from ethyl acetate giving a further 64 mg. of the racemate of (I; R<sup>1</sup> = Cl, R<sup>2</sup> = OEt), m. p. 200—202°.

Fraction (i) crystallised from ethyl acetate in prisms (70 mg., 4%), m. p. 235—237°, of the *racemate* of (*l,d*)-7-chloro-2'-ethoxy-4,6-dimethoxy-6'-methylgris-2'-en-3,4'-dione (II; R<sup>1</sup> = Cl, R<sup>2</sup> = OEt), identified by comparison of the infrared ultraviolet and n.m.r. spectra with those of the (*l,d*)-stereoisomer (see below) (Found: C, 58.8; H, 5.2; Cl, 9.8. C<sub>18</sub>H<sub>19</sub>ClO<sub>6</sub> requires C, 58.80; H, 5.2; Cl, 9.7%).

In another experiment the yield of crude solid gris-2'-en-3,4'-diones was 23%. When the Michael reaction was carried out using potassium t-butoxide (0.2 mol.) or butyl-lithium (1.0 mol) as base, no gris-2'-en-3,4'-diones were isolated.

(2) 5-Chloro-2'-ethoxy-6'-methylgris-2'-en-3,4'-dione (XVI; R<sup>1</sup> = OEt, R<sup>4</sup> = Cl, R<sup>2</sup> = R<sup>3</sup> = H). Potassium t-butoxide [from potassium (235 mg., 1.0 atom)] in diethylene glycol dimethyl ether (10 ml.) was added rapidly to a solution of 5-chlorocoumaranone (1.00 g., 1.0 mol.) and ethoxyethynyl prop-1-enyl ketone (987 mg., 1.2 mol.) in the same solvent (100 ml.) at 30°. The temperature of the red mixture rose to 33°. After storage at room temperature for 18 hr. the crude product was recovered as in (1) above.

The crude gummy product was passed through a column (13  $\times$  1.5 cm.) of alumina (acid, II) in benzene, and the gum recovered from the column was chromatographed in benzene on alumina (30  $\times$  2.0 cm., neutral, IV). Elution with benzene gave the following fractions (colours in ultraviolet light): (i) colourless fore-run giving a trace of gum on recovery; (ii) violet and blue zones (306 mg.); (iii) brown and violet zones (255 mg.); (iv) yellow zone yielding an intractable gum (33 mg.).

Fraction (ii) crystallised from ether-light petroleum (charcoal) in prisms (236 mg.) of the *gris-2'-en-3,4'-dione*, m. p. 111—112° (Found: C, 62.8; H, 5.0; Cl, 11.2, 11.3. C<sub>16</sub>H<sub>15</sub>ClO<sub>4</sub> requires C, 62.7; H, 4.9; Cl, 11.6%),  $\nu_{\max}$  ~1720, 1652, 997, 938 cm.<sup>-1</sup>,  $\lambda_{\max}$  (log  $\epsilon$ ) 223 (4.38), ~248 (4.39), 252 (4.40), 340 m $\mu$  (3.69),  $\tau$  6.13 (q, 7), 8.81 (t, 7), 4.45, 6.75—7.75 (m), 9.08 (d, 6). Rechromatography of fraction (iii) gave the same product (77 mg.).

*Homogeneity of the product.* The product (59 mg.) was chromatographed on alumina (35  $\times$  2.0 cm., neutral, II) in benzene. The column was eluted with benzene-light petroleum (b. p. 60—80°; 1 : 1) and after a fore-run (8.3 l.) the bulk of the single blue fluorescent band was collected in 500 ml. portions of eluate, yielding 6, 10, 7, and 8 mg. Further elution with benzene (500 ml. portions) yielded 7 and 1 mg. All the fractions were identical with the starting material.

The following gris-2'-en-3,4'-diones were prepared as described for the 5-chloro-analogue in (2) above, from the appropriate coumaranone (1.0 mol.), ethoxyethynyl prop-1-enyl ketone (1.2 mol), and potassium t-butoxide (1.0 mol.) in diethylene glycol dimethyl ether at 30°  $\pm$  1°. After storage for 18—20 hr. at room temperature the products were recovered and passed through a short column (A) of alumina (neutral, II) in benzene, then chromatographed in benzene on a larger column (B) of alumina (neutral, IV) in benzene. The products obtained by eluting the coloured and fluorescent zones were examined separately. The required gris-2'-en-3,4'-diones were isolated from fractions showing absorption at about 1700, 1650, and 1600 cm.<sup>-1</sup>

in the infrared spectra in Nujol. The products were triturated with ether and the resulting solid fractions were recrystallised. When pure, the gris-2'-en-3,4'-diones showed violet to purple fluorescence on alumina, but the violet colour was usually masked in the chromatograms of impure products.

(3) 2'-Ethoxy-6'-methylgris-2'-en-3,4'-dione (XVI;  $R^1 = \text{OEt}$ ,  $R^2 = R^3 = R^4 = \text{H}$ ), prepared from coumaranone (1.00 g.), was eluted from blue, brown, and yellow fluorescent zones. The gris-2'-en-3,4'-dione crystallised from ethyl acetate-light petroleum in prisms or needles (456 mg.), m. p. 111—112° (Found: C, 70.5; H, 6.0.  $\text{C}_{16}\text{H}_{16}\text{O}_4$  requires C, 70.6; H, 5.9%),  $\nu_{\text{max}}$ . 1720, 1659, 990, 932  $\text{cm}^{-1}$ ,  $\lambda_{\text{max}}$ . (log  $\epsilon$ ) 212 (4.34), 251—253 (4.47), 329  $\text{m}\mu$  (3.73).

Intractable gummy by-products were eluted from other fluorescent zones.

(4) 7-Chloro-2'-ethoxy-5,6'-dimethylgris-2'-en-3,4'-dione (XVI;  $R^1 = \text{OEt}$ ,  $R^2 = \text{Cl}$ ,  $R^3 = \text{H}$ ,  $R^4 = \text{Me}$ ), prepared from 7-chloro-5-methylcoumaranone (1.00 g.), was eluted from blue and brown zones and formed prisms (343 mg.), m. p. 126—127° (from ethyl acetate-light petroleum) (Found: C, 63.9; H, 5.3; Cl, 11.1%.  $\text{C}_{17}\text{H}_{17}\text{ClO}_4$  requires C, 63.7; H, 5.3; Cl, 11.1),  $\nu_{\text{max}}$ . ~1722, 1659, 1650, 994, 927  $\text{cm}^{-1}$ ,  $\lambda_{\text{max}}$ . (log  $\epsilon$ ) 218 (4.41), 255 (4.40), ~262 (4.35), 343  $\text{m}\mu$  (3.70),  $\tau$  6.15 (q, 7), 8.81 (t, 7), 4.47, 6.70—7.70 (m), 7.62 (5-Me), 9.08 (d, 6). The product was further chromatographed as in (2) above, but was recovered unchanged.

A yellow zone, eluted before the above grisenone, yielded a gum (254 mg.), which crystallised from ether-light petroleum in prisms, (42 mg.), m. p. 121—124°, of an unstable substance of unknown structure, which changed into a gum in a few days,  $\nu_{\text{max}}$ . (Nujol) no absorption 1650—1800  $\text{cm}^{-1}$ ,  $\nu_{\text{max}}$ . 1645sh, 1608, 1462  $\text{cm}^{-1}$ .

(5) 6-Chloro-2'-ethoxy-6'-methylgris-2'-en-3,4'-dione (XVI;  $R^1 = \text{OEt}$ ,  $R^3 = \text{Cl}$ ,  $R^2 = R^4 = \text{H}$ ), prepared from 6-chlorocoumaranone (1.00 g.), was eluted from yellow and blueish brown zones. The gris-2'-en-3,4'-dione crystallised from ether-light petroleum as needles (222 mg.), m. p. 148°, changing to 135—136° (dimorphism) on storage (Found: C, 62.7; H, 5.1; Cl, 11.6%.  $\text{C}_{16}\text{H}_{15}\text{ClO}_4$  requires C, 62.7; H, 4.9; Cl, 11.6%),  $\nu_{\text{max}}$ . ~1714, 1660, 1654, 990, 934  $\text{cm}^{-1}$ . The infrared spectra (Nujol) of the dimorphic forms was distinct, but the forms had the same infrared spectrum in solution,  $\lambda_{\text{max}}$ . (log  $\epsilon$ ) 223 (4.31), 229 (4.31), 257 (4.52), 327  $\text{m}\mu$  (3.88),  $\tau$  6.13 (q, 7), 8.80 (t, 7); 4.46, 6.70—7.80 (m), 9.08 (d, 6).

A faster-eluting blue fluorescent zone yielded an unstable solid substance (70 mg.) which did not absorb at 1650—1750  $\text{cm}^{-1}$ . Other fluorescent zones yielded gums.

(6) 7-Chloro-2'-ethoxy-6'-methylgris-2'-en-3,4'-dione (XVI;  $R^1 = \text{OEt}$ ,  $R^2 = \text{Cl}$ ,  $R^3 = R^4 = \text{H}$ ), prepared from 7-chlorocoumaranone (1.00 g.), was eluted from yellow and brown fluorescent zones and crystallised from ethyl acetate-light petroleum in prisms (259 mg.), m. p. 157—158° (Found: C, 63.0; H, 4.9; Cl, 11.3%.  $\text{C}_{16}\text{H}_{15}\text{ClO}_4$  requires C, 62.7; H, 4.9; Cl, 11.6%),  $\nu_{\text{max}}$ . ~1728, 1659, 1654, 992, 938  $\text{cm}^{-1}$ ,  $\lambda_{\text{max}}$ . (log  $\epsilon$ ) 216 (4.38), 254 (4.41), ~331  $\text{m}\mu$  (3.71),  $\tau$  6.14 (q, 7), 8.81 (t, 7), 4.46, 6.70—7.70 (m), 9.07 (d, 6).

The gris-2'-en-3,4'-dione was further chromatographed without change. Yields were increased to 20% using freshly prepared ethoxyethynyl prop-1-enyl ketone and either diethylene glycol dimethyl ether or dioxan as solvent.

A faster-eluting blue band yielded an unstable solid (49 mg.), m. p. 118—122°, which showed no max. at 1650—1800  $\text{cm}^{-1}$  in the infrared spectrum.

(b) From methoxyethynyl prop-1-enyl ketone. (1) 2'-Methoxy-6'-methylgris-2'-en-3,4'-dione (XVI;  $R^1 = \text{OMe}$ ,  $R^2 = R^3 = R^4 = \text{H}$ ). A solution of coumaranone (1.00 g., 1.0 mol.) and methoxyethynyl prop-1-enyl ketone (1.12 g., 1.0 mol.) in dioxan (90 ml.) was treated at 29° with potassium t-butoxide [from potassium (291 mg., 1.0 atom)] in diethylene glycol dimethyl ether (20 ml.). After storage for 20 hr. the product was recovered and chromatographed in the usual way. Elution of Column B with benzene removed a violet zone which yielded an intractable product (90 mg.), then a yellow, a second violet, and a yellow zone yielding 202 mg.

The latter fractions crystallised from ethyl acetate in prisms (138 mg.) of the gris-2'-en-3,4'-dione, m. p. 170° (Found: C, 69.7; H, 5.4.  $\text{C}_{16}\text{H}_{14}\text{O}_4$  requires C, 69.75; H, 5.5%),  $\nu_{\text{max}}$ . 1718, 1659, 993, 966  $\text{cm}^{-1}$ ,  $\lambda_{\text{max}}$ . (log  $\epsilon$ ) 251 (4.43), ~326  $\text{m}\mu$  (3.73).

(2) 7-Chloro-2'-methoxy-6'-methylgris-2'-en-3,4'-dione. Michael addition of methoxyethynyl prop-1-enyl ketone to 7-chlorocoumaranone (1.00 g.) was carried out in dioxan-diethylene glycol dimethyl ether as described for the preceding experiment, and the product was recovered in the usual way. Chromatography on alumina (38 × 1.2 cm., neutral III) (Column B) and elution of the column with benzene-light petroleum (b. p. 60—80°; 3:1) gave fractions: (i) yellow and grey zones yielding gums (32 mg.) on recovery; (ii) a non-fluorescent zone yielding

a gum (73 mg.) which crystallised from ethanol giving an unstable by-product, m. p. 150—151°, showing no absorption at 1650—1800  $\text{cm}^{-1}$  (this fraction was absent from some preparations); (iii) a purple zone yielding a semi-solid product (447 mg.).

Fraction (iii) crystallised from ethanol in prisms (256 mg.), m. p. 165—166°, of the *gris-2'-en-3,4'-dione* (Found: C, 61.7; H, 4.6; Cl, 12.15.  $\text{C}_{15}\text{H}_{13}\text{ClO}_4$  requires C, 61.5; H, 4.5; Cl, 12.1%),  $\nu_{\text{max}}$  1729, 1662, 994, 952, 910  $\text{cm}^{-1}$ ,  $\lambda_{\text{max}}$  (log  $\epsilon$ ) 216 (4.38), 255 (4.37), 335  $\text{m}\mu$  (3.68),  $\tau$  4.42; 6.37, 6.85—7.70 (m), 9.06 (d, 6).

The *mono-2,4-dinitrophenylhydrazone*, prepared with Brady's reagent, was an amorphous red powder, m. p. 255—258° (decomp.) (Found: N, 11.4.  $\text{C}_{21}\text{H}_{17}\text{ClN}_4\text{O}_7$  requires N, 11.85%).

(3) *2,3-Dihydro-3-oxobenzo[b]thiophen-2-spiro-1'-(2'-methoxy-6'-methylcyclohex-2'-en-4'-one)* (XVII; R = H). The Michael addition of methoxyethynyl prop-1-enyl ketone to 2,3-dihydrobenzo[b]thiophen-3-one (1.00 g.) was carried out as described in the previous experiment, the butoxide being added to the mixture of reagents at 30°. The recovered product, after passage in benzene through alumina ( $6 \times 2.7$  cm., neutral, II) was chromatographed in benzene on alumina ( $34 \times 2.3$  cm., neutral, IV). Elution of the column with benzene removed (i) pink and mauve fluorescing zones [giving intractable gums (88 mg.)], followed by (ii) brown and white zones giving semi-solid product (225 mg.). Fraction (ii) with ether gave a solid, and more solid was recovered by chromatography of the gummy mother-liquor. The combined solid product was passed through a short column of charcoal in ethyl acetate and crystallised from ether, giving pale yellow dimorphic prisms (79 mg.), m. p. 124—126° or 154—155°, of the *cyclohex-2'-en-4'-one* (Found: C, 65.6; H, 5.4; S, 11.2.  $\text{C}_{15}\text{H}_{14}\text{OS}$  requires C, 65.7; H, 5.15; S, 11.7%),  $\nu_{\text{max}}$  1705sh, 1700, 1687sh, 1658, 1652, 964, 929  $\text{cm}^{-1}$ ,  $\lambda_{\text{max}}$  (log  $\epsilon$ ) 239 (4.64),  $\sim 255$   $\text{m}\mu$  (4.41).

(4) *7-Chloro-2,3-dihydro-3-oxobenzo[b]thiophen-2-spiro-1'-(2'-methoxy-6'-methylcyclohex-2'-en-4'-one)* (XVII; R = Cl). Michael addition of methoxyethynyl prop-1-enyl ketone (4.0 g., 1.4 mol.) to 7-chloro-2,3-dihydrobenzo[b]thiophen-3-one (4.0 g., 1.0 mol.) was carried out as in the preceding experiments, and the recovered product was passed through alumina ( $12 \times 2.5$  cm., neutral, II) in benzene, and through charcoal ( $10 \times 2.5$  cm.) in ethyl acetate, then chromatographed in benzene on alumina ( $40 \times 4.0$  cm., neutral, IV). Elution of the column with benzene gave fractions: (i) a non-fluorescent zone yielding a brown intractable gum (378 mg.); (ii) violet, brown, and green zones yielding semi-solid products (2.087 g.); (iii) a brown zone yielding an intractable gum (661 mg.).

Fraction (ii) was triturated with ether and the solid part of the product was crystallised from ethyl acetate, giving pale yellow prisms (662 mg.), m. p. 195—196°, of the *cyclohex-2'-en-4'-one* (Found: C, 58.5; H, 4.3; Cl, 11.3.  $\text{C}_{15}\text{H}_{13}\text{ClO}_3\text{S}$  requires C, 58.4; H, 4.2; Cl, 11.5%),  $\nu_{\text{max}}$  1710sh, 1705, 1660, 1652, 964, 930  $\text{cm}^{-1}$ ,  $\lambda_{\text{max}}$  (log  $\epsilon$ ) 241 (4.63),  $\sim 257$   $\text{m}\mu$  (4.33).

(5) *2,3-Dihydro-1-methyl-3-oxindole-2-spiro-1'-(2'-methoxy-6'-methylcyclohex-2'-en-4'-one)* (XVIII; R = Me). Freshly prepared 2,3-dihydro-1-methylindol-3-one (1.18 g.) and methoxyethynyl prop-1-enyl ketone (1.20 g.) were dissolved in dioxan (80 ml.) under nitrogen, the solution was warmed to 32°, and a mixture of potassium t-butoxide [from potassium (327 mg.)] and diethylene glycol dimethyl ether (25 ml.) was added. After 20 hr. the crude product was recovered as described above, and was passed through alumina ( $5 \times 2.5$  cm., neutral, II) in benzene, then charcoal ( $3 \times 2.5$  cm.) in ethyl acetate. The resulting semi-solid product (1.20 g.) was chromatographed on alumina ( $40 \times 2.2$  cm., neutral, IV) in benzene. Elution of the column removed violet and dull yellow zones, giving intractable gums (145 mg.) on recovery. Elution of the following intensely fluorescent yellow band yielded a mainly solid product (825 mg.). Trituration of the latter fraction with ether, and further chromatography of material recovered from the ethereal mother-liquors, yielded the *cyclohex-2'-en-4'-one* (720 mg.), m. p. 160—162°, which crystallised from ethyl acetate-light petroleum in fluorescent yellow prisms (Found: C, 70.8; H, 6.4; N, 5.2; OMe, 11.7.  $\text{C}_{16}\text{H}_{17}\text{NO}_3$  requires C, 70.8; H, 6.3; N, 5.2; OMe, 11.4%),  $\nu_{\text{max}}$  1707sh, 1702, 1660, 1654, 976, 964  $\text{cm}^{-1}$ ,  $\lambda_{\text{max}}$  (log  $\epsilon$ ) 241 (4.59),  $\sim 255$   $\text{m}\mu$  (4.33). The product was not changed by further chromatography on alumina.

Attempted Michael addition of methoxyethynyl prop-1-enyl ketone to 2,3-dihydroindol-3-one as described for the *N*-methyl analogue yielded a complex mixture from which none of the spiran (XVIII; R = H) could be isolated.

*Reaction of Diazoethane with (1,d)-7-Chloro-4,6-dimethoxy-6'-methylgrisan-2',3,4'-trione* (XIII).—The powdered trione<sup>18,19</sup> (200 mg.) was kept in ether at 0° with an excess of ethereal diazoethane for 48 hr. The mixture was evaporated, the residue, in benzene, was washed with

aqueous sodium carbonate solution and recovered as a gum (211 mg.). The gum was chromatographed in benzene on alumina ( $31 \times 2.5$  cm., neutral, IV) and the single violet-fluorescing band was eluted with portions (250 ml.) of benzene giving fractions: (i), (ii) yielding 27 mg., m. p.  $170-182^\circ$ ; (iii)—(vi), giving mixtures (41 mg.) with a double m. p. *ca.*  $155-165^\circ$  and  $175-195^\circ$ ; (vii) (viii) 15 mg., m. p.  $175-195^\circ$ ; (ix), (x), 7 mg., m. p.  $186-198^\circ$ .

Fractions (i) and (ii) crystallised from ethyl acetate–light petroleum in prisms (20 mg.) of (1,d)-7-chloro-2'-ethoxy-4,6-dimethoxy-6'-methylgris-2'-en-3,4'-dione (II;  $R^1 = Cl$ ,  $R^2 = OEt$ ), m. p.  $181-183^\circ$  (Found: C, 59.1; H, 5.2.  $C_{18}H_{19}ClO_6$  requires C, 58.8; H, 5.2%),  $\nu_{max.} \sim 1715, 1662, 986, 958, 929, 914$   $cm^{-1}$ ,  $\lambda_{max.}$  ( $\log \epsilon$ ) 237 (4.42),  $\sim 253$  (4.25), 290 (4.37),  $\sim 320$   $m\mu$  (3.74).

Fractions (vii)—(x) from ethyl acetate–light petroleum gave prisms (17 mg.) of (1,d)-7-chloro-4'-ethoxy-4,6-dimethoxy-6'-methylgris-3'-en-3,2'-dione (XI;  $R = OEt$ ), m. p.  $200-202^\circ$  (Found: C, 59.6; H, 5.2.  $C_{18}H_{19}ClO_6$  requires C, 58.8; H, 5.2%),  $\nu_{max.}$  1714, 1659, 1655, 986, 953, 923  $cm^{-1}$ ,  $\lambda_{max.}$  ( $\log \epsilon$ )  $\sim 215$  (4.29),  $\sim 225$  (4.29), 262 (4.30), 289 (4.33), 325  $m\mu$  (3.73).

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