404. *The Constituents of Natural Phenolic Resins. Part XXIV.* A Synthesis of Galgravin.*

By J. G. Blears and R. D. Haworth.

Catalytic reduction of the furan (II) yielded the tetrahydrofuran derivative (Ia), which was isomerised to galgravin (Ib) by the action of perchloric acid.

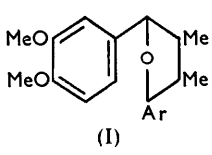
The optically inactive lignan, galgravin, was isolated from the bark of *Himantandra belgraveana* F. Muell by Hughes and Ritchie [1] who, on the basis of degradative experiments, proposed structure (I; R = Me). Since galgravin and its derivatives are optically inactive, one of the two *meso*-forms (Ia or Ib) was considered to represent the structure of the lignan. Both these *meso*-forms have now been prepared, by catalytic hydrogenation of 2 : 5-di-(3 : 4-dimethoxyphenyl)-3 : 4-dimethylfuran [2] (II) to its tetrahydro-derivative (Ia) and subsequent isomerisation to (Ib). The latter was identical with galgravin.

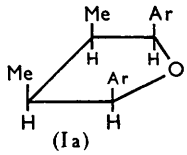
Hydrogenation of the furan (II) with a palladium oxide catalyst at room temperature and atmospheric pressure gave " dimethyl dihydroguaiaretic acid " (III) as the sole product. With a palladium–charcoal catalyst, hydrogen was absorbed very slowly and, on heating, the compound (III) was again the only product. At increased pressure at room temperature, however, reaction was considerably faster and the product was an

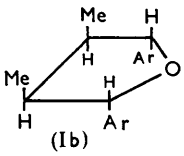
* Part XXIII, *J.*, 1955, 827.

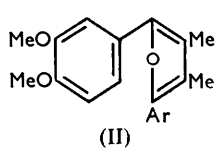
[1] Hughes and Ritchie, *Austral. J. Chem.*, 1954, **7**, 104.
[2] Atkinson and Haworth, *J.*, 1938, 1684.

optically inactive form of the tetrahydrofuran (I), which differed from galgravin and, in accordance with Linstead's views [3,4] on the stereochemistry of catalytic hydrogenation, is considered to have the *cis*-structure (Ia). This structure is sterically more compressed than the stereoisomeric (Ib), and the possibility of isomerising it to the latter was examined.

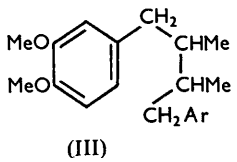

(I)

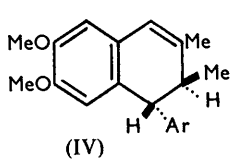

(Ia)

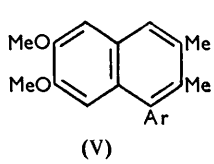

(Ib)


(II)

Ar = 3:4-$(MeO)_2C_6H_3$–


(III)


(IV)


(V)

Treatment of the compound (Ia) with sulphuric or perchloric acid in acetic acid for 6 days at room temperature gave *trans*-4-(3 : 4-dimethoxyphenyl)-3 : 4-dihydro-6 : 7-dimethoxy-2 : 3-dimethylnaphthalene (IV), m. p. 89—90°, which was readily reduced to the corresponding tetrahydronaphthalene derivative prepared previously by Muller and Vajda,[5] and was dehydrogenated to dimethyl dehydroguaiaretic acid (V). Hughes and Ritchie [1] found that galgravin was cyclised by acids to a dihydronaphthalene derivative, m. p. 81°, but we have repeated the experiment and find that the product has m. p. 89—90° and is identical with our specimen (IV).

When the tetrahydrofuran (Ia) was treated with perchloric acid in acetic acid for 30 min. at room temperature, it was converted in 42% yield into galgravin. The residual oil, probably a mixture of stereoisomers of galgravin, gave, on further treatment with perchloric acid in acetic acid, the dihydronaphthalene derivative (IV). In view of the ready reduction of the furan (II) to (III), the resistance to reduction reported for galgravin [1] appeared abnormal, and re-investigation has shown that galgravin is reduced in high yield to the same product (III) by hydrogen in presence of a palladium oxide catalyst.

The cyclisation and the isomerisation of the tetrahydrofuran (Ia) to the dihydronaphthalene derivative (IV) and galgravin (Ib) respectively involve the inversion of *cis*- to the more stable *trans*-structures, and the formula suggested for galgravin conforms to the usual lignan pattern derivable from two *trans*-coniferyl units.

In connection with this work, the methylenedioxy-analogues of (Ia and b), (II), and (III), together with 2 : 3-dipiperonyloylbutane have been prepared; the first two compounds represent the two *meso*-forms corresponding to the naturally occurring (–)-galbacin.[1]

Experimental

"Dimethyl Dihydroguaiaretic Acid" (III).—(*a*) 2 : 5-Di-(3 : 4-dimethoxyphenyl)-3 : 4-dimethylfuran [2] (II) (100 mg.) was hydrogenated in acetic acid (50 c.c.) in presence of palladium oxide (50 mg.). Filtration and removal of the solvent under reduced pressure gave an oil which on crystallisation from methanol gave dimethyl dihydroguaiaretic acid (III), m. p. and mixed m. p. 100° (dinitro-derivative, m. p. 151—152°; dibromo-derivative, m. p. 131—132°). (*b*) Galgravin (10 mg.), treated as above, gave the same product (7 mg.), m. p. 100°.

2 : 5-*Di*-(3 : 4-*dimethoxyphenyl*)*tetrahydro*-3 : 4-*dimethylfuran* (Ia).—2 : 5-Di-(3 : 4-dimethoxyphenyl)-3 : 4-dimethylfuran (II) (150 mg.) in acetic acid–methanol (1 : 1; 150 c.c.) was hydrogenated at 30 atm. in presence of 10% palladium–charcoal (25 mg.) for 15 hr. Filtration

[3] Davies and Linstead, *J.*, 1950, 1425.
[4] Linstead, Doering, Davis, Levine, and Whetstone, *J. Amer. Chem. Soc.*, 1942, **64**, 1985.
[5] Muller and Vajda, *J. Org. Chem.*, 1952, **17**, 800.

and removal of the solvent, under reduced pressure, yielded an oil which crystallised from methanol in plates, m. p. 128—130°, containing a small amount of starting material. Elution from alumina (10 g.) with benzene–ether (5 : 1) gave starting material (12 mg.) and elution with benzene–ether (3 : 2) gave 2 : 5-*di*-(3 : 4-*dimethoxyphenyl*)*tetrahydro*-3 : 4-*dimethylfuran* (105 mg.) which separated from methanol in plates, m. p. 132—133° (Found: C, 71·1; H, 7·3. $C_{22}H_{28}O_5$ requires C, 70·9; H, 7·6%). The *dinitro-derivative*, prepared in acetic acid, crystallised from methanol in pale yellow needles, m. p. 182° (Found: C, 57·1; H, 5·6; N, 6·4. $C_{22}H_{26}O_9N_2$ requires C, 57·1; H, 5·7; N, 6·1%).

trans-4-(3 : 4-*Dimethoxyphenyl*)-3 : 4-*dihydro*-6 : 7-*dimethoxy*-2 : 3-*dimethylnaphthalene* (IV).—The preceding tetrahydrofuran (100 mg.) in acetic acid (8 c.c.) containing sulphuric acid (2 drops) was kept at room temperature for 6 days, then poured into excess of dilute sodium hydroxide solution. The *product* (IV), isolated with ether, crystallised from methanol in prisms, m. p. 89—90° (Found: C, 74·5; H, 7·5. $C_{22}H_{26}O_4$ requires C, 74·5; H, 7·5%), undepressed by admixture with a specimen, m. p. 89—90°, prepared from galgravin by the same method. Reduction at atmospheric pressure and room temperature with a palladium oxide catalyst in methanol–acetic acid was complete in 2 hr.; 4-(3 : 4-dimethoxyphenyl)-1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-2 : 3-dimethylnaphthalene separated from methanol in needles, m. p. 114° (Found: C, 73·75; H, 8·0. Calc. for $C_{22}H_{28}O_4$: C, 74·1; H, 7·9%). Muller and Vajda [5] give m. p. 117°.

Galgravin (Ib).—2 : 5-Di-(3 : 4-dimethoxyphenyl)tetrahydro-3 : 4-dimethylfuran (50 mg.) was dissolved in acetic acid (1 c.c.) and a 10% solution (1 c.c.) of perchloric acid in acetic acid was added. After 30 min., the mixture was poured into dilute aqueous sodium hydroxide and extracted with ether. Removal of the solvent gave a colourless oil which, after two crystallisations from methanol, gave galgravin (21 mg.) as needles, m. p. and mixed m. p. 119·5°. The dinitro-derivative, prepared in acetic acid, crystallised from ethanol as pale yellow plates, m. p. and mixed m. p. 162—163°. The mother-liquors from the galgravin crystallisation yielded an oil, which, when treated as described for the preparation of the dihydronaphthalene derivative (IV), but with perchloric instead of sulphuric acid, gave the dihydronaphthalene (IV) (25 mg.), m. p. 89—90°.

2 : 3-*Dipiperonyloylbutane*.—1-α-Bromopropionyl-3 : 4-methylenedioxybenzene [6] (30 g.) was refluxed with copper powder (30 g.) in xylene (200 c.c.). After 25 hr. the solution was filtered and the solvent removed under reduced pressure. The residual *butane derivative* was obtained after several crystallisations from methanol as colourless plates (9 g.), m. p. 214—215° (Found: C, 67·7; H, 5·2. $C_{20}H_{18}O_6$ requires C, 67·8; H, 5·1%).

3 : 4-*Dimethyl*-2 : 5-*di*-(3 : 4-*methylenedioxyphenyl*)*furan*.—2 : 3-Dipiperonyloylbutane (40 mg.) was refluxed with methanol (20 c.c.) containing a few drops of concentrated hydrochloric acid. After this the solvent was removed, and the residue, crystallised first from acetic acid and then from methanol, yielded the *furan* as needles (35 mg.), m. p. 154° (Found: C, 71·4; H, 5·0. $C_{20}H_{16}O_5$ requires C, 71·4; H, 4·8%).

2 : 3-*Di*-(3 : 4-*methylenedioxybenzyl*)*butane*.—The preceding furan (100 mg.) was reduced as described in the preparation of " dimethyl dihydroguaiaretic acid." The product crystallised from light petroleum (b. p. 40—60°) in plates, m. p. 65—66° (lit.,[7] m. p. 70—72°). The *dibromo-derivative* crystallised from acetic acid in prisms, m. p. 136° (Found: C, 49·5; H, 4·2. $C_{20}H_{20}O_4Br_2$ requires C, 49·6; H, 4·2%).

cis-*Tetrahydro*-3 : 4-*dimethyl*-2 : 5-*di*-(3 : 4-*methylenedioxyphenyl*)*furan*, prepared in 35% yield as described above for (Ia), crystallised from methanol in needles, m. p. 94—95° (Found: C, 70·9; H, 6·4. $C_{20}H_{20}O_5$ requires C, 70·6; H, 5·9%). The *dinitro-derivative* crystallised from ethanol in yellow needles, m. p. 224° (Found: C, 55·5; H, 4·4. $C_{20}H_{18}O_9N_2$ requires C, 55·8; H, 4·2%).

The " trans- " *isomer*, prepared in 31% yield therefrom as described for galgravin, separated from methanol in prisms, m. p. 103° (Found: C, 70·2; H, 6·2%).

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THE UNIVERSITY, SHEFFIELD, 10. [*Received, December 16th*, 1957.]

[6] Ohara, *J. Pharm. Soc. Japan*, 1951, **71**, 1244.
[7] Sugimoto and Okamura, *Chem. Abs.*, 1957, **51**, 6569.