902. *Some Stereochemical Studies of Lignans.*

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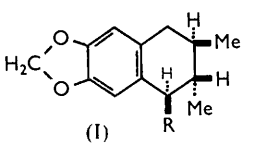
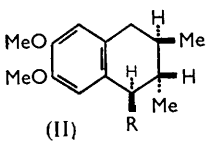
(−)-Galcatin (I) * has been converted into (−)-galbulin (II). The steric configurations of (−)-galbelgin and galgravin (isomeric forms III) have been investigated by fission of the tetrahydrofuran ring with sodium and ethanol in liquid ammonia, and examination of the products. Reduction of (±)-1 : 2- (VII) and (±)-3 : 4-dehydrogalbulin (VIII) by lithium and ammonia leads predominantly to (±)-galbulin which accordingly has the configuration (II + its enantiomer). The action of perchloric acid in acetic acid on galgravin and galbelgin has been investigated. We conclude that galgravin is probably (XII) and galbelgin probably (XIV).

The lignans (−)-galbulin (II), (−)-galbacin (III; but with R = 3 : 4-methylenedioxyphenyl), (−)-galcatin (I), galgravin, and (−)-galbelgin, the last two being stereoisomeric forms of (III), were isolated from *Himantandra* barks.[1] They offer opportunities for stereochemical studies since they carry only methyl groups instead of the oxygenated side-chains hitherto usually encountered in this series. While the present work was in progress, Schrecker and Hartwell [2] also carried out investigations in this field and arrived at some similar conclusions although by different routes.

(−)-Galcatin (I) has the same optical configuration as (−)-galbulin (II) since it can be converted into the latter by alkaline demethylenation and methylation. Schrecker and Hartwell [2] concluded on the basis of optical rotations that this relation was highly probable.


(I)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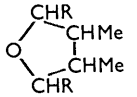
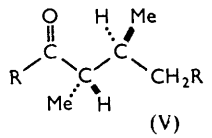
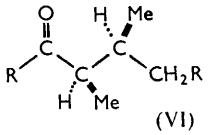
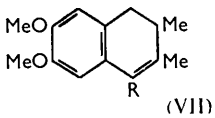
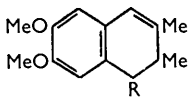

(III)

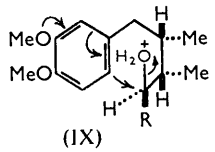
R·CH(OH)·CHMe·CHMe·CH_2R (IV)

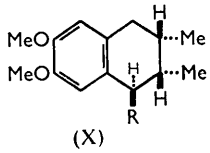

(V)


(VI)


(VII)


(VIII)


(IX)


(X)

R = 3:4-$(MeO)_2C_6H_3$

Galbelgin.—The lignan mixture from *Himantandra belgraveana* F.v.Mull. has now been found to contain the optically active lignan (III) already obtained [1] from (−)-galbacin (III; but R = 3 : 4-methylenedioxyphenyl). We have accordingly named it galbelgin. The lignan mixtures appear to differ somewhat in composition from specimen to specimen of bark; in some samples no galbelgin could be detected.

Steric Configurations of Galbelgin, Galgravin, and Galbulin.—Galgravin and galbelgin are stereoisomers (III). The former is optically inactive and so are its derivatives, and it is accordingly probably the *meso*-form since in only one case [3] has an inactive lignan been encountered where optical activity is possible. The methyl groups are therefore

* This and other formulæ represent absolute configurations, except that for (±)-forms only one form is shown.

[1] Hughes and Ritchie, *Austral. J. Chem.*, 1954, **7**, 104.
[2] Schrecker and Hartwell, *J. Amer. Chem. Soc.*, 1955, **77**, 432.
[3] Carnmalm and Erdtman, *Chem. and Ind.*, 1955, 570.

probably *cis*. In order to investigate the stereochemistry of the carbon skeleton, galgravin and galbelgin were reduced with sodium in liquid ammonia to stereoisomers (IV) which on cyclisation with perchloric acid in acetic acid gave respectively (±)-*iso*galbulin (X), m. p. 88°, and (−)-galbulin (II), m. p. 132°. Previously [4] the cyclisation of dihydrogalgravin (IV) was erroneously stated to produce an isomer of galbulin, m. p. 117°; this apparently arose from a confusion of specimens. The (±)-*iso*galbulin is structurally identical with the (+)-*iso*galbulin obtained by Schrecker and Hartwell [2] from β-conidendryl alcohol dimethyl ether. We are indebted to Dr. Hartwell for a comparison of infrared spectra: the result shows that the methyl groups are *cis*-orientated in galgravin and *trans*-orientated in galbelgin.[2] Before this was known, we had obtained indications in the same sense from other directions.

In these cyclisations the configuration of the asymmetric centre next to the hydroxyl group is unchanged. This indicates that cyclisation proceeds directly through the cation (*e.g.*, IX) rather than through an anhydro-compound.

Dihydrogalgravin (IV) on oxidation with chromic anhydride in pyridine gave the ketone dehydrodihydrogalgravin (V). In this substance there remain only the asymmetric centres associated with the methyl groups, and one of these is adjacent to the carbonyl group. Treatment with sodium ethoxide in ethanol or chromatography on alkaline alumina left the ketone unchanged. This is a strong indication that it has the sterically less compressed conformation (V) derived from the tetrahydrofuran ring (III) with *cis*-methyl groups rather than the more compressed (VI) derived from the *trans*-methyl compound. That inversion had not occurred during oxidation was shown by reduction of the ketone with lithium aluminium hydride in high yield back to dihydrogalgravin.

The isolation of (−)-dihydroguaiaretic acid dimethyl ether as a minor product in the reduction of galbelgin with sodium and liquid ammonia confirms the *trans*-orientation of the methyl groups in galbelgin. Reduction of galgravin under somewhat more drastic conditions than those previously described [4] gave a poor yield of *meso*-dihydroguaiaretic acid dimethyl ether, which is further confirmation of the *cis*-methyl groups in galgravin.

Cyclisation of the ketone (V) with polyphosphoric acid gave a (±)-1 : 2-dehydrogalbulin (VII) isomeric with the 3 : 4-dehydrogalbulin (VIII) obtained by direct cyclisation of galgravin.[1]

Dihydrogalbelgin on oxidation with chromic anhydride in pyridine apparently gave the desired ketone as shown by the spectra of the product; the ultraviolet absorption curve in particular was almost identical with that of dehydrodihydrogalgravin, the ε values being about 5% lower. The substance could not be crystallised, however, and lack of material prevented further investigation.

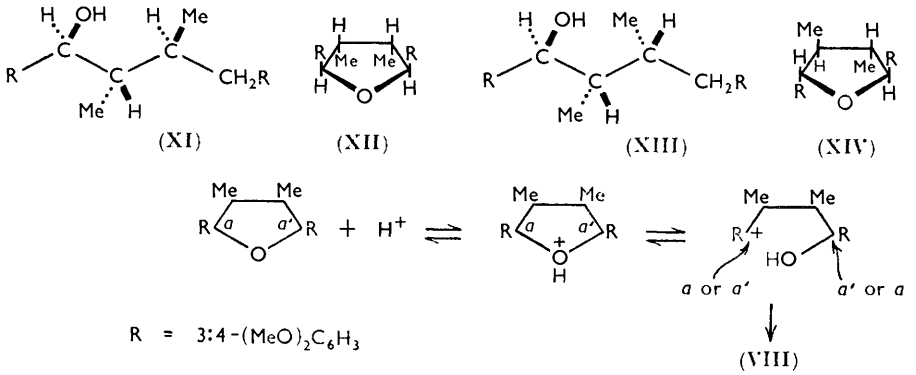
The most difficult configurations to determine in this series are those of the asymmetric centres carrying the 3 : 4-dimethoxyphenyl groups in galgravin and galbelgin; in fact, to no tetrahydrofuranoid lignan has a complete assignment been made. The problem could be approached by oxidation of the benzene rings, but we have attempted to attack it from other directions.

The reduction by lithium aluminium hydride of dehydrodihydrogalgravin (V) to dihydrogalgravin (IV = XI) would give information about the orientation of one R·CH·O· group in galgravin if its steric course were known, and of both if galgravin has the *meso*-configuration. The AlH_4^- ion should attack the least hindered side of the carbonyl group of the ketone (V),[5] producing the alcohol (XI). On this basis, and on the assumption that galgravin is a *meso*-compound (an assumption supported to some extent by the isolation of only one dihydrogalgravin from the original reduction), galgravin should be the *trans-meso*-isomer (XII). Dihydrogalgravin is oxidised 1·4—1·6 times as fast as dihydrogalbelgin by chromic anhydride in pyridine to the corresponding ketone. The oxidation

[4] Birch, Hughes, and Smith, *Austral. J. Chem.*, 1954, **7**, 83.
[5] Cram and Abdel Hafez, *J. Amer. Chem. Soc.*, 1952, **74**, 5828.

was followed in both cases by absorption at 302 mμ where the ketones absorb strongly and the alcohols weakly. Although the ketone from dihydrogalbelgin has failed to crystallise its absorption is nearly identical with that from dihydrogalgravin. This result appears to indicate that the hydrogen atom in the *H*·C·OH group of dihydrogalbelgin is more hindered sterically than the similar one in dihydrogalgravin. This conclusion follows from Westheimer's work [6] which indicates that the dominant factor in such oxidations is the degree of hindrance experienced by the hydrogen atom rather than that experienced by the hydroxyl group. The structure indicated for dihydrogalbelgin is therefore (XIII), and if it is assumed that the isolation of only one substance from the original reduction of galbelgin indicates identical steric environment for the 3 : 4-dimethoxyphenyl rings, then galbelgin has formula (XIV). If the last assumption is incorrect one other formula is possible, that with *cis*-related aromatic rings.

It is clear from models that forms (XI) and (XIII) are the thermodynamically stable ones for compounds containing *cis*- and *trans*-methyl groups respectively. This can be investigated by examining the acid-catalysed reactions of galgravin and galbelgin; we have found that the best reagent for the purpose is a dilute solution of perchloric acid in acetic acid. Reaction proceeds initially through an oxonium salt, leading to an equili-



brium of the type shown, with equilibration of the centres at *a* and *a'*, and in the present series to final irreversible cyclisation and dehydration to the naphthalene derivative (VIII).

Such reactions might be used in two ways to study the relative steric compressions in molecules of the same series. One method is to study the positions of equilibria between stereoisomers; the other is to study rates of cyclisation to compound (VIII).

The position of an equilibrium seems from models to depend chiefly on the steric compressions due to the aromatic rings in their interferences with the adjacent methyl groups or to interference of the methyl groups with each other. With both galgravin and (−)-galbelgin treatment to incipient cyclisation, as shown by increasing absorption at 280 mμ, resulted in substantial recovery of the starting material as the only crystalline product. A stereoisomer of galgravin synthesised by Haworth and Blears has been converted by a similar process of equilibration into galgravin itself,[7] which is further evidence that the latter is the stable isomer. These results again lend support to the formulations (XII) and (XIV) for galgravin and galbelgin respectively.

Rates of cyclisation to the aryldihydronaphthalene (*e.g.*, VIII) would be expected to depend on the concentration of carbonium ion, and the rate-determining stage will therefore be the fission of the oxonium ring. This in turn will be related to the steric compression in the substance equilibrated at centres *a* and *a'* if equilibration is rapid compared with cyclisation. This expectation was confirmed by the fact that the rates of cyclisation of galgravin and of Haworth and Blears's less stable isomer were found to be identical.

[6] Westheimer, *Chem. Rev.*, 1949, **45**, 419; Barton, *Experientia*, 1950, **6**, 317.
[7] Professor R. D. Haworth, personal communication.

Galbelgin cyclised at least six times more slowly than galgravin under identical conditions, cyclisation being measured by increased absorption at 280 mμ. This further supports the assumption of *trans*-methyl groups in the former and *cis*-methyl groups in the latter.

(−)-Galbacin (XIV; but R = 3 : 4-methylenedioxyphenyl) was cyclised much more slowly than galbelgin of identical configuration. This is probably due to slower fission of the oxonium salt because of smaller ability of the 3 : 4-methylenedioxyphenyl ring to stabilise the carbonium ion.

Further evidence bearing on the configuration of the 1-(3 : 4-dimethoxyphenyl) ring in galbulin (II) has been discussed by Schrecker and Hartwell.[2] It is probably *trans* to the adjacent methyl group, since the less compressed isomer would be expected from cyclisation of the intermediate cation of the type (IX).[8] This is supported by the synthesis [9] of what is almost certainly (±)-galbulin, by a series of reactions which would be expected to give the thermodynamically stable isomer at each stage. Further evidence is now provided by reduction with lithium in liquid ammonia of the isomeric dehydrogalbulins (VII) and (VIII); crystalline (±)-galbulin was isolated in over 50% yield in each case as the only crystalline product. It must be the thermodynamically stable *trans-trans*-isomer (II) since it is clear from models that there is no likelihood of formation of a less stable isomer by a kinetically controlled reaction (cf. ref. 10).

Finally, catalytic hydrogenation of *cyclo*galgravin [(±)-3 : 4-dehydrogalbulin (VIII)] under mild conditions might be expected to cause the methyl group attached to the new asymmetric centre to assume the *cis*-relation to the bulky 1-(3 : 4-dimethoxyphenyl) ring. Hydrogenation in alcoholic solution with palladium–charcoal in fact gives (±)-galbulin, m. p. 116—117°. All the evidence therefore points to the *trans-trans*-structure (II) for this substance.

Experimental

Conversion of Galcatin into Galbulin.—Galcatin (1·8 g.) and a solution from sodium (1·5 g.) in methanol (30 c.c.) were heated in a glass-lined autoclave at 150—170° for 12 hr. Methylation of the phenolic product with methyl sulphate and sodium hydroxide gave a gum with which the methoxide treatment and methylation were repeated. The product (1 g.) crystallised from methanol and had m. p. 130—132° undepressed by authentic (−)-galbulin (m. p. 132°).

Isolation of Galbelgin.—The mother-liquors from the crystallisation of galgravin [1] gave on slow evaporation two obviously different kinds of crystal. These were separated by hand-picking: one lot was galgravin, m. p. 121°; the other was identical with the product obtained [1] by demethylenation and methylation of (−)-galbacin and had m. p. 138°, $[\alpha]_D$ −102° (*c* 0·04 in chloroform). In this case the ratio of total galgravin to galbelgin was about 30 : 1.

Dihydrogalgravin and Dihydrogalbelgin.—The reduction with sodium and ethanol in liquid ammonia of galgravin has been described.[4] Galbelgin (600 mg.) in ethylene glycol dimethyl ether (20 c.c.) and liquid ammonia (25 c.c.) was reduced by addition of sodium (125 mg.). After 7 min. a blue colour still persisted and was discharged by the addition of a few drops of ethanol followed by water (2 c.c.). The ammonia was removed and the product extracted with ether. It partially crystallised and the solid was recrystallised from methanol to give (−)-dihydroguaiaretic acid dimethyl ether, $[\alpha]_D^{24}$ −24° (*c* 0·26 in chloroform), m. p. 88° undepressed by an authentic specimen. The infrared spectra were also identical. The recorded values [2] are m. p. 86—87°, $[\alpha]_D$ −31° (*c* 1·52 in chloroform). The yield was only a few mg. The main bulk of *dihydrogalbelgin* crystallised from the methanol mother-liquors after dilution with water and, recrystallised from aqueous ethanol (300 mg.), had m. p. 104°, $[\alpha]_D$ −94° (*c* 1·0 in chloroform) (Found: C, 70·2; H, 8·0. $C_{22}H_{30}O_5$ requires C, 70·6; H, 8·0%). This substance (100 mg.) in ethanol (5 c.c.) and concentrated hydrochloric acid (1 c.c.) was left for 3 days. Dilution with water and crystallisation from ethanol gave (−)-galbulin, m. p. 130—131° (Found: C, 73·6; H, 8·1. Calc. for $C_{22}H_{28}O_4$: C, 74·1; H, 7·9%).

Dihydrogalgravin similarly treated gave (±)-*iso*galbulin, $[\alpha]_D$ 0°, m. p. 88° (Found: C, 73·8;

[8] Haworth and Slinger, *J.*, 1940, 1321; 1942, 448.
[9] Muller and Vajda, *J. Org. Chem.*, 1952, **17**, 800.
[10] Birch, Smith, and Thornton, *J.*, 1957, 1339; Birch, Smith, and Wilson, unpublished work.

H, 7·8. Calc. for $C_{22}H_{28}O_4$: C, 74·1; H, 7·9%). The infrared spectrum of its chloroform solution is identical with that of (+)-*iso*galbulin.

Conversion of Galgravin into meso-*Dihydroguaiaretic Acid Dimethyl Ether.*—Galgravin 750 mg.) in " dimethyloxitol " (ethylene glycol dimethyl ether) (10 c.c.) and liquid ammonia (50 c.c.) was reduced by adding sodium (about 6 equivs.) until the blue colour persisted for 10 min. Ethanol (1 c.c.) was added, followed by water. The product was worked up in the usual way and the fraction least soluble in aqueous ethanol proved to be *meso*-dihydroguaiaretic acid dimethyl ether (60 mg.), m. p. 101°, undepressed by an authentic specimen (m. p. 102°) which had an identical infrared spectrum. The mother-liquor yielded some dihydrogalgravin, but a gum was also present.

Dehydrodihydrogalgravin.—Dihydrogalgravin (400 mg.) in pyridine (5 c.c.) was added to chromic anhydride (400 mg.) and pyridine (3 c.c.). Next morning the mixture was added to water and extracted with ether which was washed with dilute hydrochloric acid. The resulting *dehydrodihydrogalgravin* (340 mg.), crystallised from ethanol, had m. p. 105°, $\lambda_{max.}$ 229, 275, 302 mμ (log ε 4·42, 4·13, 3·92), $\lambda_{min.}$ 247, 294 mμ (log ε 3·45, 3·92), $\nu_{max.}$ 1675 cm.$^{-1}$ (Found: C, 70·6; H, 7·6. $C_{22}H_{28}O_5$ requires C, 71·0; H, 7·5%). This material depressed the m. p. of the starting material and its infrared spectrum contained no hydroxyl band. Attempts to isomerise it with 5% ethanolic sodium ethoxide at 20° during 3 weeks, or on the steam-bath for 2 hr., gave only a substantial recovery of ketone, m. p. and mixed m. p. 102—105°.

Similar oxidation of dihydrogalbelgin gave only a gum, but the infrared band at 1675 cm.$^{-1}$, the lack of a hydroxyl band, and identity of the ultraviolet spectrum with that above (ε 95% of those given) showed that oxidation had resulted.

Comparative oxidations of dihydrogalgravin and dihydrogalbelgin were carried out side by side with the same reagents. Finely powdered chromic anhydride (150 mg.) was added to " AnalaR " pyridine (5 c.c.). After 3 minutes' shaking, portions (1·00 c.c.) were added to samples (10 mg.) of the two alcohols. After an arbitrary time (0·5—5 hr.) the partially oxidised products were extracted and the quantity of ketone estimated by its ultraviolet absorption at 302 mμ (dehydrodihydrogalgravin log ε 3·92). In all experiments the galbelgin derivative was oxidised more slowly. The rates appeared to depend greatly on the particular sample of reagent. The following are typical results of two runs at successive times:

	Run I			Run II		
Dehydrodihydrogalbelgin	7	35	81%	38	44	63%
Dehydrodihydrogalgravin	10	50	100%	48	65	98%

(±)-1 : 2-*Dehydrogalbulin.*—Dehydrodihydrogalgravin (150 mg.) was rapidly stirred into a mixture of phosphoric acid (1 c.c.) and phosphoric oxide (1 g.) at 70° and the temperature raised during 1 min. to 90°; then water (5 c.c.) was added. Extraction with ether and crystallisation from ethanol gave (±)-1 : 2-*dehydrogalbulin*, m. p. 116° (Found: C, 74·5; H, 7·5. $C_{22}H_{26}O_4$ requires C, 74·6; H, 7·4%). Some unchanged starting material was recovered. With longer heating considerable dehydrogenation occurred to the phenylnaphthalene derivative,[1] m. p. 178°.

Reduction of Dehydrodihydrogalgravin.—Dehydrodihydrogalgravin (50 mg.) and lithium aluminium hydride (50 mg.) in pure ether (20 c.c.) were left at room temperature with occasional shaking for 30 min. A little ethyl acetate was added, the mixture poured into water, and the product extracted with ether. After crystallisation from aqueous methanol, the product (40 mg.), m. p. 108°, was identified as dihydrogalgravin by mixed m. p. and infrared spectra.

Attempted Isomerisations of Galgravin and Galbelgin.—The lignan was treated with 1·2% solution of perchloric acid in acetic acid at room temperature until the presence of cyclised material was shown by increased light absorption at 280 mμ. Working up afforded only a substantial amount of starting material.

*Cyclisations of Galgravin, Galbelgin, and the all-*cis(?)-*Isomer.*—The lignans were treated as above (0·1% solution in acetic acid) and the extent of cyclisation calculated from the absorptions at 280 mμ: galgravin, galbelgin log ε 3·82; *cyclo*-derivatives $\lambda_{max.}$ 280 mμ (log ε 4·17) [also found is a peak at $\lambda_{max.}$ 225 mμ (log ε 4·55)]. *cyclo*Galbelgin [(−)-3 : 4-dihydrogalbulin] had m. p. 97—98°, $[\alpha]_D$ +125° (*c* 0·85 in chloroform) (Found: C, 74·7; H, 7·3. Calc. for $C_{22}H_{26}O_4$: C, 74·6; H, 7·4%). The relative rates of cyclisation, measured at small conversions, and on the basis of unimolecular kinetics are: galgravin 1·0; galbelgin 0·17; all-*cis*(?)-isomer (m. p. 133°) 1·0. Under identical conditions galbacin cyclised at a relative rate <0·02 ($\lambda_{max.}$ 287 mμ).

Reduction of (±)-**1** : **2**- *and* (±)-**3** : **4**-*Dehydrogalbulin.*—Lithium (10 mg.) was added to (±)-**1** : **2**-dehydrogalbulin (95 mg.) in dry ether (2 c.c.) and liquid ammonia (20 c.c.). The solution became first scarlet, and then deep blue. After 5 min. solid ammonium chloride was cautiously added, followed by water (5 c.c.). Ether-extraction, followed by crystallisation of the product from aqueous ethanol, gave (±) galbulin (50 mg., 53%), m. p. 117°, identified by mixed m. p. and infrared spectrum.

(±)-**3** : **4**-Dehydrogalbulin (*cyclo*galgravin), m. p. 88—89° (100 mg.), similarly reduced gave (±)-galbulin (55 mg.), m. p. 117°.

Hydrogenation of (±)-**3** : **4**-dehydrogalbulin (100 mg.) with palladium–charcoal in ethanol gave (±)-galbulin (70 mg.), m. p. 116—117°.

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