Tetrahedron, 1965, Vol. 21, pp. 1495 to 1499. Pergamon Press Ltd. Printed in Northern Ireland

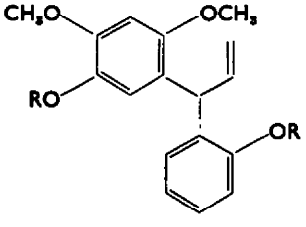
# CONSTITUTION OF LATIFOLIN

DARSHAN KUMARI, S. K. MUKERJEE and T. R. SESHADRI
Department of Chemistry, Delhi University, India

(*Received* 12 *December* 1964; *in revised form* 23 *February* 1965)

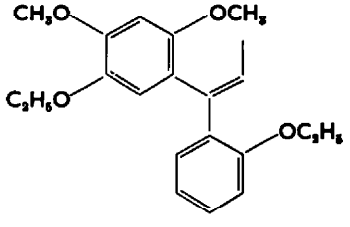
**Abstract**—The positions of the hydroxy groups of latifolin have been established by preparing its ethyl ether and subjecting it to degradation in stages to (i) isolatifolin diethyl ether (ii) dimethoxy diethoxy benzophenone. The constitution of the benzophenone has been established by synthesis as 2,4-dimethoxy-2',5-diethoxybenzophenone. Using Grignard reaction the synthetic benzophenone has been converted into $\gamma$-(2,4-dimethoxy-5-ethoxyphenyl)-$\gamma$-(2'-ethoxyphenyl) propene which was identical with isolatifolin diethyl ether.

LATIFOLIN,[1] the chief constituent of the heartwood of *Dalbergia latifolia* was previously shown to have two hydroxyl groups, two methoxyl groups and a diphenylallyl system. The constitution of the dimethyl ether was definitely established in the earlier publication. Although it was definite that one of the two hydroxyl groups was a single substituent on a phenyl ring, yielding salicylic acid on oxidation, the location of the other hydroxyl group (with reference to the two methoxyl groups) was not definite. A tentative assignment could however be made based on the following considerations: (1) analogy with dalbergin in which the free hydroxyl is in the 6 position, corresponding to the 5 position of latifolin, (2) the IR spectrum with two different —OH frequencies suggesting difference in location, the higher frequency attributable to the 2'-hydroxyl and the lower to the 5-hydroxyl which is affected by chelation with the neighbouring methoxyl group. The correctness of assignment of position 5 for the second hydroxyl group (formula Ia) has now been proved by both degradative and synthetic experiments with the diethyl ether (Ib).




I

a, R = H
b, R = $C_2H_5$



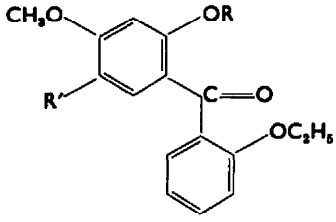

II

*Degradation experiments.* The diethyl ether (Ib), obtained in good yield by ethylation with diethyl sulphate, was first isomerized by base into isolatifolin diethyl ether (II). Use of strong aqueous alkali, *n*-butanolic potassium hydroxide and potassium t-butoxide in t-butanol was found to be unsatisfactory. Heating at high temp with mono-sodio derivative of ethylene glycol in the same solvent led to decomposition.

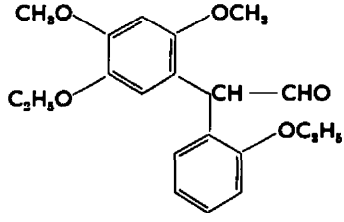
[1] S. BALAKRISHNA, M. M. RAO and T. R. SESHADRI, *Tetrahedron* **18**, 1503 (1962).

However sodamide in boiling toluene gave a cleaner product from which, after chromatography on a column of silica gel impregnated with silver nitrate,[2] the propenyl isomer (II) could be obtained in about 50% yield. This was found to be identical with a synthetical sample of γ-(2,4-dimethoxy-5-ethoxyphenyl)-γ-(2′-ethoxyphenyl) propene the preparation of which is mentioned later. The UV absorption spectra of latifolin diethyl ether and isolatifolin diethyl ether do not differ to any appreciable extent. Since the compounds are otherwise pure, this feature may be due to lack of effective conjugation between the double bond and the benzene rings probably produced by steric factors.

For the degradation of the propenyl isomer to the benzophenone (IIId), however, it was not necessary to use the pure compound (II). The crude gum obtained from sodamide treatment was ozonized and the products directly converted into their 2,4-dinitrophenylhydrazones. Chromatography on neutral alumina separated a small amount of gummy yellow D.N.P. identified by paper chromatography as acetaldehyde derivative and a red crystalline D.N.P. identical with that of IIId prepared synthetically as mentioned later. The corresponding derivative of IV expected to arise from unchanged Ib could not be obtained in spite of a careful search.

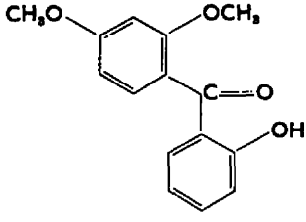



III

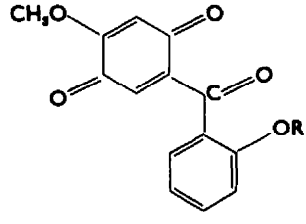



IV

a, $R = R' = H$
b, $R = H$; $R' = OH$
c, $R = H$; $R' = OC_2H_5$
d, $R = CH_3$; $R' = OC_2H_5$
e, $R = CH_3$; $R' = H$
f, $R = CH_3$; $R' = OCH_3$
g, $R = C_2H_5$; $R' = OC_2H_5$




V




VI

a, $R = C_2H_5$
b, $R = CH_3$

*Synthetic experiments.* In attempts to prepare the diethoxy compound (IIId), although Hoesch reaction between resorcinol and *o*-ethoxybenzonitrile failed, Friedel and Crafts reaction between resorcinol dimethyl ether and *o*-ethoxybenzoyl chloride

[2] A. S. GUPTA and S. DEV, *J. Chrom.* **12**, 189 (1963).

gave a good yield of a monohydroxy benzophenone along with a minor proportion of a neutral benzophenone which can have only structure IIIe. Since the monohydroxy benzophenone on methylation gave the same neutral product (IIIe), it should be 2-hydroxy-4-methoxy-2′-ethoxybenzophenone (IIIa) and not the isomeric ketone (V). Persulphate oxidation of IIIa gave the quinol (IIIb) in fair yield but the partial ethylation of it proved difficult. When one molar proportion of ethyl sulphate was used, the compound was recovered even after heating for 24 hr. Use of large excess and long time gave the diethylated product. However a large excess and shorter reaction time gave a mixture of partially ethylated product and unchanged quinol which were separated using very dilute sodium hydroxide. This difficulty of partial ethylation is probably due to steric effect of bulkier ethoxyl group which reduces chelation between the *o*-hydroxy and the carbonyl group and diminishes the difference between the two hydroxyls of the quinol system. It may be mentioned here that the corresponding partial methylation of 2,5-dihydroxy-2′,4-dimethoxybenzophenone proceeds in a smooth manner (unpublished work). The quinol (IIIb) by oxidation with nitric acid (*d.* 1·2) gave a quinone (VIa) whose UV spectrum was different from that of the quinone obtained from the analogous 2′-methoxybenzophenone (VIb).

The partial ethyl ether (IIIc) was methylated to the diethoxy dimethoxy ketone (IIId) in good yield and its 2,4-dinitrophenylhydrazone was undepressed in m.p. when mixed with that of the ketone obtained from the ozonolysis of isolatifolin diethyl ether.

Condensation of IIId with ethylmagnesium bromide followed by dehydration of the product yielded $\gamma$-(2,4-dimethoxy-5-ethoxy phenyl)-$\gamma$-(2′-ethoxyphenyl) propene (II) identical in mixed m.p., UV and IR with isolatifolin diethyl ether, thus confirming the structure of latifolin as given in I. Further work on synthetical lines is in progress.

## EXPERIMENTAL

*Latifolin diethyl ether* (Ib)

Latifolin (10 g) was refluxed for 12 hr with diethyl sulphate (20 ml), anhydrous $K_2CO_3$ (50 g) and acetone (200 ml). After filtration and removal of the acetone, the excess diethyl sulphate was decomposed with water. The solid product was extracted with ether and the extract washed with NaOH aq (1%, 100 ml) and then with water and the ether evaporated; the residue crystallized from EtOH as colourless stout prisms m.p. 68°. (Found: C, 73·5; H, 8·0; $C_{21}H_{26}O_4$ requires: C, 73·6; H, 7·6%.) $\lambda_{max}^{EtOH}$ 280 m$\mu$ (log $\epsilon$ 3·74), 290 m$\mu$ (log $\epsilon$ 3·70).

*Isolatifolin diethyl ether* (II)

A solution of latifolin (2 g) in dry toluene (100 ml) containing powdered sodamide (5 g) was heated under reflux for 12 hr. After filtering through glass wool, the toluene solution was concentrated under red. press., cooled and treated with EtOH (5 ml). On evaporation of the solvent mixture again under red. press. a gummy product was obtained. The solid left on the glass wool was added cautiously in small lots to crushed ice and the resulting gummy product was mixed with the earlier one, taken up in ether, the solution dried and passed through a short column of neutral alumina. The column was washed with pet. ether (40–60°, 150 ml), the washings concentrated to a small volume and kept in the refrigerator for 1 day when a crystalline deposit (400 mg) m.p. 64°–78° was obtained. Repeated crystallization from MeOH gave a sample m.p. 75°–78° but thin layer chromatography showed it to be a mixture. Final purification was achieved by chromatography of this solid (100 mg) on a column of silica gel impregnated with $AgNO_3$ (10 g) and elution with a mixture of ether and pet. ether (1:1, 200 ml). Evaporation of ether left a solid (55 mg) which crystallized from MeOH as colourless stout rectangular prisms m.p. 82·5–83°. (Found: C, 73·3; H, 7·6; $C_{21}H_{26}O_4$ requires C, 73·6; H, 7·6%.) $\lambda_{max}^{EtOH}$ 290 m$\mu$ (log $\epsilon$ 3·77).

*Ozonolysis of isolatifolin diethyl ether* (II)

A steady stream of ozonized $O_2$ was passed for 10 min through a cooled (−10°) solution of the crude compound (100 mg) in dry ethyl acetate (10 ml). After attaining room temp, the solution was shaken with pre-reduced Pd—C (5%; 25 mg) in an atmosphere of $H_2$ till the rapid absorption of $H_2$ ceased. Removal of the catalyst and evaporation of the solvent left a glassy residue which was directly converted into 2,4-dinitrophenylhydrazone by treatment with the reagent in alcoholic HCl solution. After extraction with chloroform, the total dinitrophenylhydrazones were chromatographed on a column of neutral alumina. Elution with a mixture of benzene and pet. ether (1:9) gave a small amount of yellow first fraction which did not crystallize but paper chromatography showed it to be a mixture of D.N.P. of (i) acetaldehyde and (ii) formaldehyde by comparison with authentic samples. Further elution of the column with benzene–pet. ether (7:3) gave the major product as a red band, which crystallized from ethyl acetate as tiny red prisms, m.p. 182–183°. A mixed m.p. of this sample with a synthetic sample of the dinitrophenylhydrazone of 2,4-dimethoxy-2′,5-diethoxybenzophenone was undepressed. (Found: C, 59·2; H, 5·4; $C_{25}H_{26}O_8N_4$ requires: C, 58·8; H, 5·1%.)

2-*Hydroxy-4-methoxy-2′-ethoxybenzophenone* (IIIa)

*o*-Ethoxybenzoyl chloride (25 g) in dry ether (50 ml) was added dropwise (2 hr) to an ice cold and shaken solution of resorcinol dimethyl ether (19·5 g) and anhydrous $AlCl_3$ (40 g) in dry ether (100 ml). After 12 hr, the mixture was poured over crushed ice (500 g) and HCl aq (50 ml) and then heated in a boiling water bath for 1 hr. The cooled mixture was extracted with ether and the ether extract washed successively with (a) sat. NaH $CO_3$ aq and (b) NaOH aq (10%, 3 × 100 ml). On acidification (b) gave the above ketone (15 g) which was extracted with ether and crystallized from MeOH when it was obtained as colourless hexagonal prisms, m.p. 77–78°. (Found: C, 70·2; H, 6·1; $C_{16}H_{16}O_4$ requires: C, 70·6; H, 5·9%.) It gave a light brown colour with alcoholic $FeCl_3$; $\lambda_{max}^{MeOH}$ 282 mμ (log ε 4·20), 322 mμ (4·10).

The ether solution left after extraction with NaOH gave 2,4-dimethoxy-2′-ethoxybenzophenone (IIIe) which was purified by percolation through short column of neutral alumina in benzene–pet. ether (1:9). It came out from MeOH as colourless thin plates, m.p. 82–83°. (Found: C, 71·8; H, 6·7; $C_{17}H_{18}O_4$ requires: C, 71·3; H, 6·3%.) $\lambda_{max}^{MeOH}$ 278 mμ (log ε 3·90), 310 mμ (log ε 4·01). This (190 mg) was also obtained when the hydroxybenzophenone (200 mg) was refluxed with acetone (10 ml), dimethyl sulphate (0·4 ml) and anhydrous $K_2CO_3$ (1 g).

2,5-*Dihydroxy-4-methoxy-2′-ethoxybenzophenone* (IIIb)

A saturated solution of potassium persulphate (6 g) in water was added dropwise to a well stirred solution of 2-hydroxy-4-methoxy-2′-ethoxybenzophenone (4 g) in pyridine (10 ml) and NaOH aq (50 ml, 4%) over a period of 2 hr at room temp and kept overnight. The mixture was acidified to Congo-red and the precipitated solid was filtered off. The filtrate was extracted with ether in order to remove traces of unchanged ketone. It was then strongly acidified with conc. HCl (100 ml) and heated to 80° for 30 min to complete the hydrolysis. After cooling, the precipitated solid (1·2 g) was filtered and washed with water; it crystallized from EtOH as light yellow needles, m.p. 168–169°. (Found: C, 66·0; H, 6·0; $C_{16}H_{16}O_5$ requires: C, 66·6; H, 5·5%.) It gave green colour with $FeCl_3$. Light absorption data: $\lambda_{max}^{EtOH}$ 243 mμ (log ε 4·19) 286 mμ (log ε 4·07), 355 mμ (log ε 4·30). The diacetate obtained by treatment with acetic anhydride and pyridine for 1 hr crystallized from dil. EtOH as colourless aggregates of small prisms, m.p. 130–131°. (Found: C, 64·5; H, 5·5; $C_{20}H_{20}O_7$ requires: C, 64·5; H, 5·4%.)

2-*Methoxy*-5-(2′-*ethoxybenzoyl*)*benzoquinone* (VIa)

On heating a suspension of the quinol (100 mg) in $HNO_3$ (*d* 1·2; 10 ml) to 50°, it dissolved and an orange substance quickly came out. After 15 min, the product was collected and crystallized from ethyl acetate–pet. ether yielding orange prisms, m.p. 152–153°. (Found: 66·6; H, 5·4; $C_{16}H_{14}O_5$ requires: C, 67·1; H, 4·9%.) It gave a dark red colour with alcoholic NaOH and green colour with conc. $H_2SO_4$; $\lambda_{max}^{EtOH}$ 260 mμ (log ε 4·16), 315 mμ (log ε 3·52).

2-*Methoxy*-5-(2′-*methoxybenzoyl*) *benzoquinone* (VIb) was prepared in the same manner as VIa from 2,5-dihydroxy-4,2′-dimethoxybenzophenone [$\lambda_{max}^{MeOH}$ 243 mμ (4·01), 284 mμ (3·91), 355 mμ (3·91)], obtained from 2-hydroxy-4,2′-dimethoxybenzophenone by persulphate oxidation. It crystallized from ethyl acetate as yellow thin rectangular prisms m.p. 160° $\lambda_{max}^{EtOH}$ 255 mμ (log ε 4·18), 292 mμ (log ε 3·51).

*2-Hydroxy-4-methoxy-2',5-diethoxybenzophenone* (IIIc)

The quinol IIIb (0·5 g) was refluxed for 4 hr with acetone (50 ml), diethyl sulphate (1 ml; excess) and $K_2CO_3$ (10 g). After working up in the usual manner, the product was taken up in ether and the ether solution extracted successively with (a) NaOH aq (0·5%; 3 × 50 ml) till there was no dark red colour due to quinol dianion and (b) stronger NaOH aq (5%, 4 × 50 ml). On acidification (a) gave unchanged quinol (200 mg) and (b) yielded the partial ethyl ether (220 mg) which crystallized from MeOH as light yellow stout rectangular prisms m.p. 66–67°. (Found: C, 68·0; H, 6·3; $C_{19}H_{20}O_5$. requires: C, 68·4; H, 6·3%.). The substance gave a dark green colour with alcoholic $FeCl_3$.

*2,4,5-Trimethoxy-2'-ethoxybenzophenone* (IIIf)

On refluxing the quinol IIIb (100 mg) with dimethyl sulphate (1 ml) and $K_2CO_3$ (4 g) in acetone (20 ml) for 8 hr and crystallization of the product from MeOH, the trimethyl ether was obtained as colourless thin rhombic plates, m.p. 82–83°. (Found: C, 68·6; H, 6·7; $C_{18}H_{20}O_5$ requires: C, 68·4; H, 6·4%.)

*2,2',5-Triethoxy-4-methoxybenzophenone* (IIIg)

(a) The quinol IIIb (200 mg) gave the triethyl ether on heating with excess diethyl sulphate and $K_2CO_3$ in acetone for 24 hr. The product crystallized from MeOH as pale yellow stout rectangular prisms m.p. 120–122°. (Found: C, 70·1; H, 7·3; $C_{20}H_{24}O_5$ requires: C, 69·7; H, 7·0%.)

(b) A solution of the quinol (IIIb) diacetate (420 mg) and diethyl sulphate (2 ml) in MeOH (15 ml) was added dropwise with stirring to NaOH aq (20 ml, 10%). A crystalline solid separated after 20 min; it was collected and purified on a short column of alumina in ether solution. Crystallization from MeOH gave the product identical in every respect with the triethyl ether described above.

*2,4-Dimethoxy-2',5-diethoxybenzophenone* (IIId)

Methylation of 2-hydroxy-2',5-diethoxy-4-methoxy benzophenone (300 mg) with dimethyl sulphate (1 ml) and anhydrous $K_2CO_3$ (5 g) in acetone (20 ml) was complete after refluxing for 24 hr. The product (280 mg) crystallized from EtOH as colourless hexagonal stout tablets, m.p. 91–93°. (Found: C, 69·5; H, 6·9; $C_{19}H_{22}O_5$ requires: C, 69·1; H, 6·7%.) Its 2,4-dinitrophenylhydrazone crystallized from benzene pet. ether as deep red tiny prisms, m.p. 182°.

*γ-(2,4-Dimethoxy-5-ethoxy phenyl)-γ-(2'-ethoxyphenyl) propene* (II)

Grignard reagent prepared from EtBr (0·3 ml) and Mg (80 mg) in dry ether (10 ml) was treated dropwise and with stirring with a solution of 2,4-dimethoxy-2',5-diethoxybenzophenone (100 mg) in dry ether (20 ml). The mixture was refluxed for 2 hr and was left overnight. The solution was then acidified with dil $H_2SO_4$ and extracted with ether. The residue obtained on evaporation of ether was heated under reflux for 30 min in alcohol (10 ml) containing a trace of conc. $H_2SO_4$. After dilution with water the product was extracted with ether. It crystallized from MeOH as colourless stout rectangular prisms m.p. 82–83° alone or mixed with a sample of isolatifolin diethyl ether. These two products had the same UV and IR spectra.

*Acknowledgements*—Our thanks are due to C.S.I.R. for the grant of fellowship to D. K.