SYNTHESIS OF ANGOLENSIN

By V. N. Gupta and T. R. Seshadri, F.A.Sc.

(*Department of Chemistry, University of Delhi, Delhi-8*)

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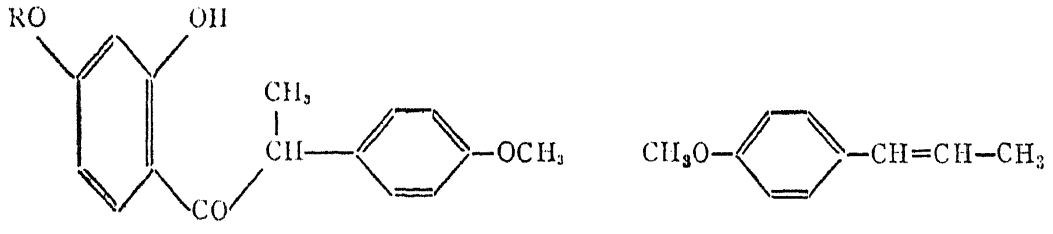
Angolensin (I *a*), an α-methyl-desoxy benzoin related to isoflavones, was first isolated by King, King and Warwick[1] from the wood of *Pterocarpus angolensis* and later by Gupta and Seshadri[2] from the wood and bark of *Pterocarpus indicus*. Its consitution (I *a*) was established by degradative studies by King *et al.*[1] but no synthetic support was provided. An obviously simple synthesis would be the C-methylation of the reactive methylene group of 2 : 4-dihydroxy-4′-methoxy-desoxy benzoin. Badcock *et al.*[3] have shown that when heated with excess of methyl iodide and anhydrous potassium carbonate in acetone solution 2-hydroxy-4-methoxy- and 2-hydroxy-4 : 6-dimethoxy desoxy benzoins suffer α-methylation besides O-methylation. But when there was a methoxyl group in the benzyl part no C-methylation took place. This reaction has now been examined in detail using various modifications and has not been found to be suitable for the present synthesis.

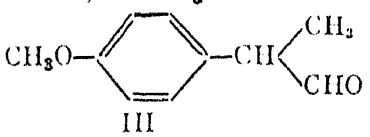


I

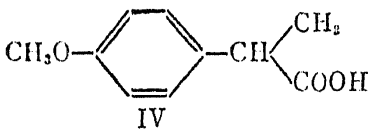
a; R = H

b; R = CH_3

II



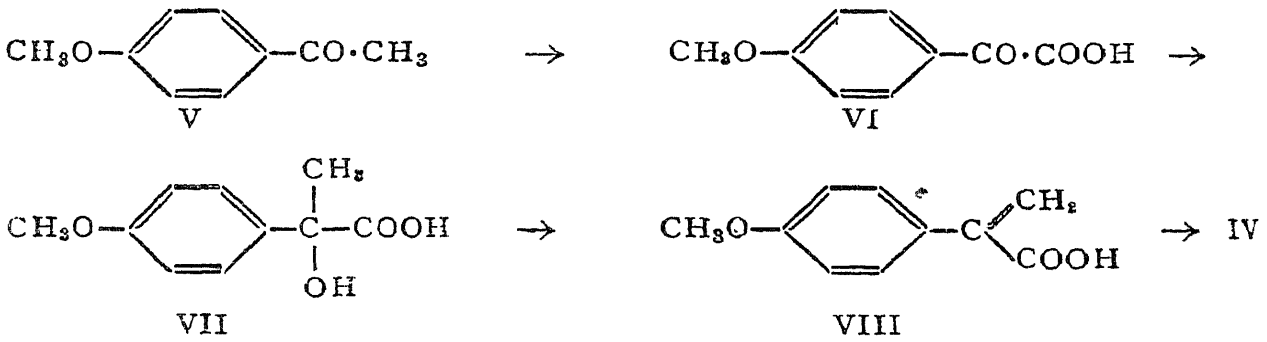
III



IV

Consequently an alternative method involving Friedel and Craft's reaction has been examined. *p*-Methoxy-hydratropic acid (IV) was needed for this purpose. This was originally prepared by Bougault[4] by the oxidation of anethole (II) first with iodine and mercuric oxide to *p*-methoxy-hydratropaldehyde (III) and then with silver oxide and alkali to *p*-methoxy hydratropic acid (IV). He reported that in many oxidations of the aldehyde to the acid the whole of the product got resinified. This has been our experience also. Hence the C-methylation of the ester and the nitrile of *p*-methoxy phenyl acetic acid was attempted with methyl iodide in the same way as with phenyl-acetonitrile and ethyl phenylacetate using sodamide[5] and also using sodium methoxide in methanol and anhydrous potssium carbonate in acetone

solution but the reactions were unsuccessful. This may be attributed to the adverse effect of the *p*-methoxyl group on the ionisation of the active methylene group. Finally the synthesis of *p*-methoxy-hydratropic acid (IV) has been conveniently carried out by the following route.



For the oxidation of *p*-methoxy-acetophenone (V) to *p*-methoxyphenyl glyoxalic acid (VI) with alkaline potassium permanganate a modification of the method of Bougault[6] has been employed giving a good yield. The second stage has been conveniently carried out by the Grignard reaction using methyl magnesium iodide in ether. *p*-Methoxy-atrolactinic acid (VII) was then dehydrated to *p*-methoxy-atropic acid (VIII) by following the procedure of Bougault[7] and final reduction to *p*-methoxy-hydratropic acid (IV) was accomplished using sodium amalgam and water.

The feasibility of Friedel and Craft's reaction using *p*-methoxy-hydratropic acid chloride was first tested using resorcinol dimethyl ether when angolensin-4-methyl ether (I *b*) was obtained satisfactorily and it agreed in its properties with the earlier description of King *et al.*[1] and with the sample prepared in this laboratory[2] from natural angolensin. Repetition of Friedel and Craft's reaction using O-dibenzyl resorcinol followed by debenzylation yielded angolensin (I *a*) identical with the racemic form of angolensin isolated from the wood of *Pterocarpus indicus*.[2]

EXPERIMENTAL

p-*Methoxy Phenyl Glyoxalic Acid (VI)*

This acid was first obtained by Bougault[6] by alkaline potassium permanganate oxidation of *p*-methoxy acetophenone in aqueous suspension at 0°. Owing to sparing solubility of the ketone the yield is poor. The following modified procedure gives a much better yield.

A solution of potassium permanganate (32 g.) and potassium hydroxide (12 g.) in water (600 c.c.) was added dropwise to a solution of *p*-methoxy acetophenone (12 g.) in pyridine (100 c.c.) at 15° with stirring during a period of four hours. The stirring was continued for one hour more and the unreacted permangante decomposed with sodium bisulphite. Manganese

dioxide that had separated was filtered off and washed with two 100 c.c. portions of water. The alkaline filtrate was acidified with concentrated hydrochloric acid (200 c.c.) and the solution left overnight in a refrigerator. Impure anisic acid (about 1 g.) that had separated out was filtered off, the filtrate saturated with sodium chloride, the solution extracted repeatedly with ether and the ether solution dried over magnesium sulphate. The residue after evaporation of ether crystallised from benzene-petroleum ether mixture as colourless thin and large rectangular plates, m.p. 87–88°. Yield, 6–7 g.

p-Methoxy-Atrolactinic Acid (VII)

This acid was obtained by Bougault[7] by permanganate oxidation of *p*-methoxy-hydratropic acid (IV). It has now been obtained from *p*-methoxy-phenyl glyoxalic acid (VI) by the Grignard reaction.

Magnesium powder (1·6 g., 3 mols) was added to a solution of methyl iodide (4·2 c.c.; 3 mols) in dry ether (100 c.c.) containing a trace of iodine. When the metal had completely dissolved, the ether solution was cooled to 0° and added dropwise to a solution of *p*-methoxy glyoxalic acid (4 g., 1 mol) in dry ether (100 c.c.) cooled in freezing mixture. After two hours standing in the freezing mixture a gummy solid was found to have separated out. The ether was decanted off and the solid treated with ice and dilute sulphuric acid when slowly it turned crystalline. It was extracted repeatedly with ether and the ether extract dried over magnesium sulphate. The residue after evaporation of ether crystallised from benzene as colourless prismatic needles and narrow rectangular plates, m.p. 129–30°.

p-Methoxy-Atropic Acid (VIII)

The following represents the best conditions for obtaining this acid by the method of Bougault.[8] A solution of *p*-methoxy-atrolactinic acid (5 g.) in glacial acetic acid (50 c.c.) was refluxed in an oil-bath at 130° for four hours. Acetic acid (about 40 c.c.) was distilled off under reduced pressure, the residue diluted with water (90 c.c.) and left at 0° for 24 hours when *p*-methoxy-atropic acid crystallised as colourless very thin plates, m.p. 118–20°. Yield, 2·5 g. A solution of the substance in glacial acetic acid decolorised bromine water.

p-Methoxy-Hydratropic Acid (IV)

Sodium amalgam (50 g., 2·5%) was added with constant shaking to a solution of *p*-methoxy-atropic acid (1 g.) in 2% aqueous sodium hydroxide (50 c.c.) and was left overnight. The brown alkaline solution was separated from mercury and acidified with concentrated hydrochloric acid when a semi-solid mass separated out which was repeatedly extracted with ether and the ether solution dried over magnesium sulphate. After the distillation of ether

the residue crystallised from benzene-petroleum ether mixture as colourless irregularly-shaped plates, m.p. 55–57°. Yield, 0·8 g. It did not decolorise bromine water in glacial acetic acid solution.

Angolensin-4-methyl Ether (*I b*)

The chloride of *p*-methoxy hydratropic acid (IV) was prepared as follows: To a solution of the acid (2 g.) in dry chloroform (25 c.c.) was added phosphorus trichloride (0·6 g., 1/3 mol.) dropwise with shaking and cooling. The reaction mixture was left at room temperature for two hours with occasional shaking, heated to 60° for two minutes and the chloroform solution separated from the phosphorous acid that had separated. On distilling off chloroform under reduced pressure the acid chloride was left behind as a very pale yellow viscous oil which was directly used for the Friedel and Craft's reaction.

A solution of anhydrous aluminium chloride (8 g.) was prepared in dry ether (80 c.c.) with cooling in ice. To this was added resorcinol dimethyl ether (1·6 g.) and then an ether solution of the acid chloride prepared as above. The mixture was left at room temperature overnight. The next day as much of ether as possible was distilled off, the complex decomposed with ice and hydrochloric acid and extracted with ether. The ether solution was separated into aqueous sodium bicarbonate soluble fraction (A), sodium carbonate soluble fraction (B), sodium hydroxide soluble fraction (C) and the neutral fraction (D). Fraction (A) gave a small amount of unchanged acid; fraction (B) gave none on acidification and fraction (D) yielded a small amount of resorcinol dimethyl ether and hence all these were rejected. Fraction (C) on acidification gave a viscous oil which was extracted with ether and the ether solution dried over sodium sulphate. The residue left after removal of ether was distilled under reduced pressure when angolensin-4-methyl ether passed over at 230–33° at 2·3 mm. pressure. It gave a reddish brown colour with alcoholic ferric chloride and a green colour with concentrated nitric acid. Yield, 1·2 g. King *et al.*[1] recorded 240–50° as bath temperature at 0·3 mm. pressure.

The filter-paper chromatography of synthetic angolensin-4-methyl ether and the one prepared from natural angolensin by the procedure of Gupta and Seshadri[2] gave the same brown ring, R_F, 0·83 at 36° using 15% isopropyl alcohol as the solvent and diazotised benzidine reagent as the developer. The oxidation of synthetic angolensin-4-methyl ether with potassium permanganate in acetone solution was carried out by the procedure of Gupta and Seshadri[2] whereby *p*-methoxy-acetophenone, anisic acid and *p*-methoxy salicylic acid were isolated.

Angolensin (I a)

Using the same procedure and resorcinol dibenzyl ether (3·2 g.) and the acid chloride from *p*-methoxy-hydratropic acid (2 g.) crude angolensin-4-benzyl ether was obtained. Yield, 0·5 g. Small amounts of unchanged acid and resorcinol dibenzyl ether were recovered but the poor yield should be ascribed to the resinification that takes place during the reaction.

The benzyl ether (0·5 g.) was dissolved in glacial acetic acid (20 c.c.) and concentrated hydrochloric acid (20 c.c.) added. The mixture was heated on a boiling water-bath for one hour, poured over ice and extracted repeatedly with ether. The ether extract was washed with aqueous sodium bicarbonate to remove acetic acid and then extracted with 5% aqueous sodium carbonate. The carbonate solution was acidified, extracted with ether and the ether solution dried over sodium sulphate. The residue after removal of ether crystallised from benzene-petroleum ether mixture as small prisms and plates, m.p. 118–20° alone or admixed with an authentic sample of racemic angolensin isolated from *Pterocarpus indicus*.[2] It gave a reddish brown colour with alcoholic ferric chloride, R_F, 0·72 (brown ring) at 36° using the organic layer of methanol-chloroform-ligroin-water (1 : 2 : 7 : 5) mixture as the solvent and diazotised benzidine reagent as the developer was obtained with both synthetic and natural samples and with a mixture of the two.

Summary

By the Friedel and Craft's reaction using resorcinol dimethyl ether and *p*-methoxy hydratropic acid chloride, angolensin monomethyl ether has been prepared. Employing resorcinol dibenzyl ether for the reaction and final debenzylation, angolensin (racemic) itself has been obtained.

References

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