CONSTITUTION OF GOSSYPIN

Part III. Ethylation of Gossypin and Conversion into Ethyl-tambuletin

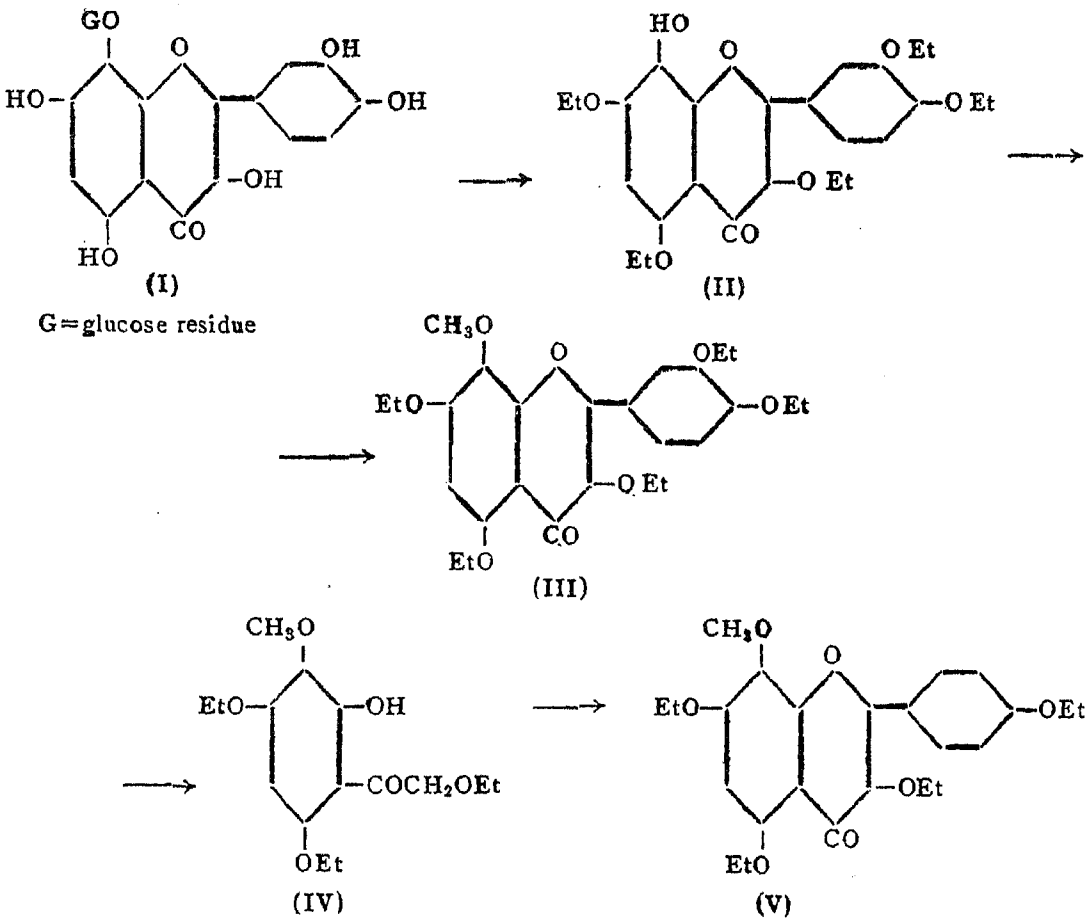
BY K. VISWESWARA RAO AND T. R. SESHADRI, F.A.SC.

(From the Department of Chemistry, Andhra University, Waltair)

Received July 15, 1947

ETHYLATION of hydroxyl groups does not appear to have been used as freely as methylation in the investigation of the structure of organic compounds. In several cases it is especially useful and brings about considerable simplification. As recent examples may be quoted the study of the naturally occurring partial methyl ethers of flavonols, patuletin,[1] calycopterin,[2] oroxylin-A[3] and tambuletin[4] and also of those obtained from the degradation of gossypin,[5] cannabiscitrin[6] and populnin.[7] Its applicability to the glucosides themselves appeared to merit attention particularly since the ethylation products could be correlated with those obtained from the partial methyl ethers. A few glucosides of flavonols have now been examined in this connection. Ethyl iodide has been used successfully in the past for the ethylation of the free flavonols and the partial methyl ethers. But it is not found to be suitable for the glycosides probably because of its poor activity. Diethyl-sulphate has therefore been employed and it works very satisfactorily. The ethylation of gossypin[5] is described here as a typical example.

Gossypin (I) undergoes ethylation readily by means of diethyl sulphate and anhydrous potassium carbonate in dry acetone medium and the product yields on hydrolysis a pentaethyl-ether of gossypetin (II) with a free hydroxyl group. It resembles the corresponding pentamethyl-ether[5] in its properties. When it is methylated, a compound (III) is obtained with a methoxyl in the place of the glucosidoxy group the other hydroxyl groups being ethylated. This compound is useful since it can be converted into tetra-ethyl tambuletin (V) thus confirming the relationship between gossypin and tambuletin, the former being the 8-glucoside of gossypetin and the latter the 8-methyl ether of herbacetin. For this purpose compound (III) is subjected to fission with alcoholic potash whereby O-diethyl-protocatechuic acid and gossypetol-triethyl-monomethyl-ether (IV) are obtained. The ketone (IV) is then condensed with the anhydride and sodium salt of *p*-ethoxy-benzoic acid. The transformations are represented below:



Experimental

O-Pentaethyl-gossypetin (II).—

Finely powdered gossypin (2 g.) was suspended in anhydrous acetone (100 c.c.) and treated with diethyl sulphate (10 c.c.) and potassium carbonate (25 g.). The mixture was refluxed for 48 hours, filtered and the potassium salts thoroughly washed with hot acetone. The filtrate was distilled to recover the solvent and the reddish brown oily liquid left behind was refluxed for 2 hours with dilute sulphuric acid (7%). On cooling the deep red solution a brown solid was obtained which was filtered off and washed with water. Yield 1 g. Crystallisation from alcohol gave pale yellow stout rectangular prisms melting at 145–47°. (Found: C, 63·7; H, 6·4; $C_{25}H_{30}O_8$, H_2O requires C, 63·2; H, 6·7%.) It was readily soluble in alcohol and the solution gave only a pale brown colour with ferric chloride. In dilute aqueous sodium hydroxide it readily dissolved to a yellow solution but in stronger alkaline solutions the solid assumed an orange colour and remained undissolved due to the formation of a sparingly soluble salt.

The above hydroxy compound (0·1 g.) was acetylated using acetic anhydride (3 c.c.) and a few drops of pyridine. The acetate crystallised

from alcohol in the form of colourless rectangular prisms melting at 147–48°.

8-Methyl-3:5:7:3′:4′-pentaethyl-ether of gossypetin (III).—

A solution of the above pentaethyl-ether of gossypetin (1 g.) in anhydrous acetone (30 c.c.) was treated with dimethyl sulphate (1 c.c.) and potassium carbonate (5 g.). The mixture was refluxed for 6 hours, the solvent was distilled off and the residue treated with water. The undissolved colourless solid was filtered off, washed with water and purified by crystallising first from alcohol and subsequently from a mixture of benzene and petroleum ether. It crystallised in the form of colourless broad rectangular plates melting at 140–42°. (Found: C, 66·2; H, 6·4; $C_{26}H_{32}O_8$ requires C, 66·1; H, 6·8%.) It was insoluble in aqueous sodium hydroxide and did not give any colour with ferric chloride.

Alkaline hydrolysis of methyl-ethyl-gossypetin (III).—

The above sample of methyl-ethyl-gossypetin (1 g.) was refluxed with absolute alcoholic potash (30 c.c. of 8% solution) for 6 hours. The solvent was then distilled off as much as possible and the residue treated with water (100 c.c.). The clear brown solution was acidified with concentrated hydrochloric acid and saturated with sodium chloride. The colourless crystalline solid that separated out was filtered and washed with a little water. It was treated with saturated aqueous sodium bicarbonate, filtered and washed with water. The filtrate (F) was preserved for the examination of the acid. The residue was dried and crystallised from a mixture of benzene and petroleum ether when the ketone (IV) separated out as colourless broad rectangular plates melting at 125–26°. (Found: C, 60·2; H, 7·5; $C_{15}H_{22}O_6$ requires C, 60·4; H, 7·4%.) It was readily soluble in alcohol and benzene and sparingly in ether and petroleum-ether. In alcoholic solution it gave a reddish violet colour with ferric chloride.

The bicarbonate filtrate (F) was acidified when a white crystalline solid separated out. It was filtered, washed with water and crystallised from aqueous alcohol. It came out in the form of colourless long rectangular rods melting at 167–68° alone or in admixture with an authentic sample of the diethyl-ether of protocatechuic acid.

p-Ethoxy-benzoic anhydride.—

A solution of *p*-ethoxy-benzoic acid (5 g.) in a mixture of anhydrous pyridine (15 c.c.) and anhydrous ether (100 c.c.) was cooled to 0° and treated with thionyl chloride (2 c.c.) in small quantities. After keeping in the ice-chest for 3 hours with occasional stirring the reaction mixture was stirred

with crushed ice and ice-cold hydrochloric acid. The colourless solid that separated out was filtered off. On distilling off the ether in the filtrate some more of the material was obtained. The total quantity was successively triturated with cold hydrochloric acid and cold sodium carbonate solution, filtered, washed with water and dried over concentrated sulphuric acid in a vacuum desiccator. Yield 4 g. Crystallisation of the product from benzene yielded colourless broad hexagonal plates melting at 110–12°. (Found: C, 68·5; H, 5·7; $C_{18}H_{18}O_5$ requires C, 68·8; H, 5·7%.)

8-*Methoxy*-3:5:7:4′-*tetraethoxy-flavone*: (O-*tetraethyl tambuletin V*).—

An intimate mixture of the ketone (IV) (0·4 g.), *p*-ethoxy-benzoic anhydride (1 g.) and sodium *p*-ethoxy benzoate (0·8 g.) was heated under reduced pressure at 170–80° for 3 hours. The reaction product was cooled and refluxed for 10 minutes with 10% alcoholic potash (30 c.c.). The solvent was distilled off under reduced pressure, the residue treated with water and the whole extracted twice with ether. On distilling off the ether a crystalline solid was obtained which was purified by crystallisation from a mixture of ether and petroleum-ether whereby it separated out as colourless rectangular plates melting at 110–12°. Mixed melting point with the tetraethyl-ether obtained from tambuletin[4] was not depressed.

Summary

Gossypin has been ethylated and hydrolysed. The resulting penta-ethyl ether of gossypetin is further methylated and the product converted into tetra-ethyl tambuletin by alkali fission and condensation of the ketonic product with the anhydride and sodium salt of *p*-ethoxy benzoic acid. This confirms the relationship between gossypin and tambuletin.

References

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5. Rao and Seshadri .. *Ibid.*, 1947, **25**, 397.
6. Seshadri and Venkateswarlu *Ibid.*, 1946, **23**, 29.
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