

SYNTHETIC COMPOUNDS RELATED TO THE CARDIAC GLYCOSIDES

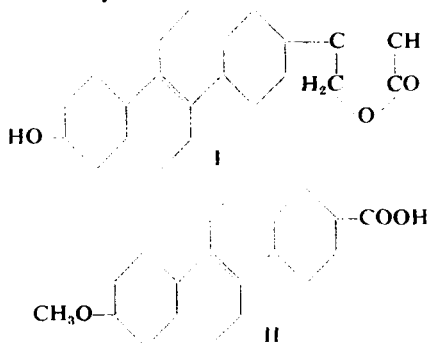
PART II

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IN Part I of this series the *p*-hydroxyphenyl- $\Delta\alpha:\beta$ -butenolide and its β -glucoside were found to have no cardiac activity.¹ The success which has attended the use of the stilbene nucleus in the preparation of synthetic oestrogens naturally encourages the use of this nucleus in other fields of steroid derivatives. For this reason it was decided to attempt the preparation of a 4-hydroxy-4'- $\Delta\alpha:\beta$ -butenolido- $\alpha:\beta$ -diethylstilbene (I) in the hope that this molecule or the glucoside prepared from it would exhibit the desired activity.



Some little difficulty was encountered in the preparation of this compound, but at length its methyl ether was obtained. The starting point of the synthesis was, 4-methoxy- $\alpha:\beta$ -diethylstilbene-4'-carboxylic acid (II) which had been previously obtained in low yields by Jaeger and Robinson² and by Neher and Miescher³, and therefore attempts were made to improve this preparation. The previous authors obtained (II) by the hydrolysis of the corresponding nitrile although difficulties had previously been encountered in the hydrolysis of such stilbene derivatives^{4,5,6}.

This difficulty was surmounted by the hydrolysis of 4-methoxy-4'-cyanodeoxybenzoin² with a mixture of acetic and sulphuric acids, when a good yield of 4-methoxy-4'-carboxy-deoxybenzoin was obtained in colourless needles melting at 223° to 224°C. It was slightly soluble in alcohol, ether and benzene. This acid was converted into its ethyl ester which, was obtained in fine white needles melting at 136° to 137°C. It gave the required analytical figures as did its 2:4-dinitrophenylhydrazone which crystallised from benzene-light petroleum mixture in red scales m.pt. 165° to 166°C.

The above ester was ethylated by means of sodium ethoxide in ethyl alcohol and the 4-methoxy-4'-carbethoxy- α -ethyl-deoxybenzoin obtained

was purified by distillation *in vacuo*; it formed a pale yellow oil boiling at 220° to 223°C./0.2 mm. Hg. pressure. The 2:4-dinitrophenylhydrazone separated as an oil and could not be induced to crystallise. The ester was easily hydrolysed to the free acid which, separated as an oil and solidified into a resinous mass which was subsequently crystallised from benzene-light petroleum mixture in thick needles melting at 125° to 126°C. Both the ester and the acid gave analytical figures according with those theoretically required.

The resulting 4-methoxy-4'-carbethoxy- α -ethyldeoxybenzoin was treated with ethyl magnesium iodide to yield the corresponding tertiary alcohol, but during the final distillation involved in the purification of the isolated product, water was eliminated from the molecule and ethyl 4-methoxy- α : β -diethylstilbene-4'-carboxylate was isolated in good yield and quantitatively hydrolysed to the desired stilbene acid (II). The conversion of this stilbene acid into the corresponding acid chloride was effected without difficulty with thionyl chloride and, without isolation, the product was treated with diazomethane to give the diazoketo derivative which, on warming with glacial acetic acid yielded 4-methoxy-4'- ω -acetoxyacetyl- α : β -diethylstilbene. This compound appeared as a thick oil boiling at 208° to 211°C. (bath temperature)/0.1 mm. Hg. pressure and formed a crystalline 2:4-dinitrophenylhydrazone melting at 232° to 233°C. Both the ketone and its dinitrophenylhydrazone gave the required analytical figures.

The above compound was treated with ethyl bromoacetate in presence of zinc to give the required lactone 4-methoxy- α : β -diethylstilbene- Δ^{α} : β -butenolide in the form of pale microcrystalline powder melting at 94° to 95°C. It gave a positive Legal's test, and the analytical figures accorded with the theoretical requirements.

Unexpected difficulty was encountered in the attempts made to demethylate this stilbene-butenolide and further work is in progress to achieve this end and then to convert the demethylated substance into its glucoside.

Preliminary pharmacological examination, for which we are indebted to Professor Buttle and Dr. Dyer of the Pharmacological Department of this School, indicated that the lethal dose for guinea-pigs was about 200 mg./kg.; the death was characteristic of the cardiac aglucones which suggests that the compound possessed approximately 1/1000 the potency of strophanthidin. This result is encouraging because it is more than probable that the demethylated compound would possess a much higher level of activity. Again the conversion of the compound into its glucoside would in all probability produce a further increase in activity. This work is therefore being continued in order to obtain the glucoside which might be expected to exhibit a reasonable level of activity.

EXPERIMENTAL

4'-Carboxy-4-methoxydeoxybenzoin. 4-Methoxy-4'-cyanodeoxybenzoin² (2.5 g.) was dissolved in glacial acetic acid (20 ml.), sulphuric acid (20 ml.) and water (20 ml.) were added and the mixture boiled under

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reflux for 4 hours. The cooled mixture was diluted with water and filtered, and the precipitate recrystallised from 60 per cent. acetic acid. The acid was obtained in colourless needles. It is slightly soluble in alcohol, ether and benzene, m.pt. 223° to 224°C. Yield 82 to 85 per cent. Found C, 71.0; H, 5.13 per cent.; $C_{17}H_{14}O_4$ requires C, 71.11; H, 5.19 per cent.

Esterification of the acidic group. Hydrogen chloride was passed into a boiling alcoholic solution of the acid (2 g.) for 4 hours. The solution was concentrated under reduced pressure and the ester, which crystallised out, was filtered off and recrystallised from 90 per cent. alcohol. It formed fine white needles, m.pt. 136° to 137°C. Yield 85 per cent. Found C, 71.15; H, 6.14 per cent.; $C_{18}H_{15}O_4$ requires C, 72.50; H, 6.04 per cent. The 2:4-dinitrophenylhydrazone crystallised from benzene-light petroleum mixture as red scales, m.pt. 165° to 166°C. Found C, 60.34; H, 4.00; N, 11.1 per cent. $C_{24}H_{22}N_4O_7$ requires C, 60.00; H, 4.00; N, 10.2 per cent.

4'-Carbethoxy-4-methoxy- α -ethyldeoxybenzoin. 4'-Carbethoxy-4-methoxydeoxybenzoin (5.5 g.) was mixed with absolute alcohol (50 ml.) and the mixture raised to boiling. A solution of sodium ethoxide (0.5 g. of sodium in 10 ml. of alcohol) was added and after 10 minutes boiling, ethyl iodide (3 g.) was added and the mixture strongly boiled for 10 minutes more. Sodium ethoxide solution (0.25 g. of sodium in 6 ml. of alcohol) was added followed by ethyl iodide (1 g.). After 2 hours refluxing, another addition of sodium ethoxide (0.25 g. of sodium and 6 ml. of alcohol) and ethyl iodide (1 g.) was made and the whole refluxed for 6 hours. To isolate the desired compound, the neutral solution was diluted with water, acidified with dilute sulphuric acid and extracted with ether. The ethereal extract was washed with aqueous sodium carbonate, sodium thiosulphate solution and water respectively, then dried over anhydrous sodium sulphate. The residue remaining after the removal of ether was distilled under reduced pressure. 4'-Carbethoxy-4-methoxy- α -ethyldeoxybenzoin distilled as a pale yellow oil at 220° to 223°C./0.2 mm. Hg. pressure. Yield 90 per cent. Found C, 73.9; H, 6.91 per cent.; $C_{20}H_{22}O_4$ requires C, 73.6; H, 6.61 per cent.

The 2:4-dinitrophenylhydrazone separated as a semisolid mass which could not be crystallised.

Hydrolysis. The ester (1 g.) was boiled with 10 per cent. sodium hydroxide solution (20 ml.) for 1 hour, when it completely dissolved. Treatment of the clear solution with dilute sulphuric acid produced a milky precipitate, which solidified into a resinous mass. It was crystallised from a mixture of benzene and light petroleum in clusters of thick needles, m.pt. 125° to 126°C. Found C, 71.93; H, 5.77 per cent.; $C_{18}H_{18}O_4$ requires C, 72.50; H, 6.04 per cent.

4'-Carbethoxy-4-methoxy- α : β -diethylstilbene. An ethereal solution of ethyl magnesium iodide prepared from ethyl iodide (17.26 g.) and magnesium turnings (2.23 g.) in ether in the usual way, was added with stirring to a solution of 4'-carbethoxy-4-methoxy- α -ethyldeoxybenzoin

(10 g.) in dry ether (100 ml.), with continual stirring during the addition and for 1 hour more. The mixture, carefully protected from moisture, was left overnight and then refluxed for 2 hours. It was then cooled and decomposed by means of ice and hydrochloric acid; the oil that separated was extracted with ether, the ethereal extract dried over anhydrous magnesium sulphate, and the ether then removed. The residue was distilled *in vacuo* and the fraction boiling at 180° to 183°C/0.2 mm. Hg. pressure was collected. It formed a colourless thick oil and its solution in carbon tetrachloride decolorised bromine. Found C, 78.4; H, 7.77 per cent.; $C_{20}H_{22}O_3$ requires C, 78.1; H, 7.71 per cent.

4-Methoxy-4'-carboxy- α : β -diethylstilbene. The above ester (5 g.) was boiled with a mixture of alcohol (10 ml.) and 10 per cent. aqueous sodium hydroxide (10 ml.) for 1 hour. On cooling, the sodium salt of the acid crystallised out. It was filtered off and boiled with glacial acetic acid (20 ml.), when 4-methoxy-4'-carboxy- α : β -diethylstilbene separated in colourless needles on cooling, m.pt. 175° to 176°C. Yield 96 per cent.

4-Methoxy-4'- ω -acetoxyacetyl- α : β -diethylstilbene. 4-Methoxy- α : β -diethylstilbene-4'-carboxylic acid (5 g.) was dried by heating on a water-bath under reduced pressure for 2 hours. The dry acid was converted to its acid chloride by refluxing with thionyl chloride (20 g.) for 4 hours. On removal of the excess of thionyl chloride, the acid chloride remained as a semisolid mass, which was dissolved in ether and added at 0°C. to an ethereal solution of diazomethane⁷ prepared from 60 g. of nitrosomethyl urea⁸. The mixture was kept at 0°C. for 1 hour, then at room temperature for 16 hours. Ether was removed under reduced pressure and the crude diazoketone thus obtained, mixed with glacial acetic acid (20 ml.) and heated on a water-bath for 2 hours after which no more nitrogen was evolved. The mixture was cooled, diluted with ether, shaken with water and then with sodium carbonate solution. The ethereal layer was separated and dried over calcium chloride; on removal of the ether, the ketol acetate was left as a thick oil, which was purified by distillation *in vacuo*. It distilled at 208° to 211°C. (bath temperature)/0.1 mm. Hg. pressure. Yield 70 per cent. Found C, 74.00; H, 6.8 per cent.; $C_{21}H_{24}O_4$ requires C, 75.4, H, 7.1 per cent.

The 2:4-dinitrophenylhydrazone, crystallised from alcohol in the form of an orange microcrystalline powder, m.pt. 233° to 234°C. Found C, 63.60; H, 5.37; N, 10.01 per cent.; $C_{28}H_{20}O_4N_4$ requires C, 63.73; H, 5.5; N, 10.25 per cent.

4-Methoxy- α : β -diethylstilbene-4'- $\Delta\alpha'$: β' -butenolide. Zinc (2 g.) was added to a solution of 4-methoxy-4'- ω -acetoxyacetyl- α : β -diethylstilbene (3 g.) in benzene (20 ml.) and the mixture raised to boiling on a water-bath. Ethyl bromoacetate (3 g.) in benzene (10 ml.) was then gradually added to the boiling mixture with stirring. After 2 hours refluxing and stirring, the reaction mixture was cooled and decomposed by means of ice and concentrated hydrochloric acid. The benzene layer was separated, washed with water and sodium carbonate solution respectively and dried over anhydrous sodium sulphate. After removing the benzene under

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reduced pressure, the residue was heated on a water-bath under reduced pressure for half an hour, then mixed with a 50 per cent. solution of hydrobromic acid in glacial acetic acid and heated again for another half hour, and finally poured into a large volume of ice-cold water. The precipitate that formed was filtered and recrystallised from benzene. It formed pale yellow crystals, m.pt. 94 to 95°C. Yield 24 per cent. Found C, 79.8; H, 6.74 per cent.; $C_{22}H_{24}O_8$ requires C, 79.31; H, 6.92 per cent. The compound gave a positive Legal's test.

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