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CHEMICAL EXAMINATION OF *WEDELIA CALENDULACEAE*—IV

SYNTHETIC ANALOGUES OF WEDELOLACTONE

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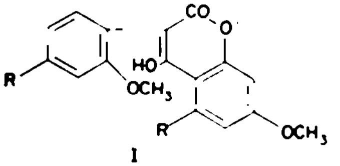
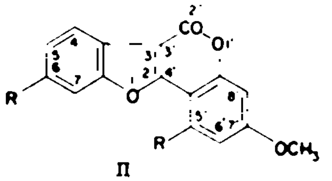
Abstract—The syntheses of 7′-methoxy- and 5′,7′,6-trimethoxy-coumarino(3′,4′:3,2)coumarones (IIa and IIb) are described.

SOME time ago we had isolated a crystalline substance named wedelolactone from the fresh leaves of *Wedelia calendulaceae*.[1] The structure of this compound as 5′,5,6-trihydroxy-7′-methoxy-coumarino(3′,4′:3,2)coumarone was proved by degradation[2] as well as by synthesis of its tri-O-methyl ether.[3] Subsequently Bickoff *et al.*,[4] reported the isolation from ladino clover of an estrogenic substance, coumestrol which was shown to be 6,7′-dihydroxycoumarino(3′,4′:3,2)coumarone by degradation as well as by synthesis. It was of interest to prepare some analogous compounds for comparative pharmacological tests,[5] so that the structural features necessary for estrogenic activity may be revealed. As part of the programme, we have synthesised 7′-methoxy- and 5′,7′,6-trimethoxycoumarino(3′,4′:3,2)coumarones (IIa and IIb) by the route employed in the synthesis of tri-O-methylwedelolactone.[3]

Condensation of 2-hydroxy-4-methoxyphenyl *o*-methoxybenzyl ketone[6] with diethyl carbonate and pulverized sodium afforded in satisfactory yield 4-hydroxy-7-methoxy-3(*o*-methoxyphenyl)-coumarin (Ia). The latter, on treatment with pyridine hydrochloride followed by subsequent methylation, gave 7′-methoxycoumarino-(3′,4′:3,2)coumarone (IIa). Likewise 5′,7′,6-trimethoxycoumarino(3′,4′:3,2)coumarone (IIb) was obtained from the corresponding coumarin (Ib) by fusion with pyridine hydrochloride followed by methylation.



I
a: R = H
b: R = OCH$_3$



II
a: R = H
b: R = OCH$_3$

In an earlier publication,[2] we had reported the reduction of the compound III by

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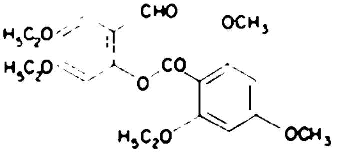
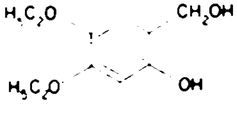
[1] T. R. Govindachari, K. Nagarajan and B. R. Pai, *J. Chem. Soc.* 629 (1956).
[2] T. R. Govindachari, K. Nagarajan, B. R. Pai and P. C. Parthasarathy, *J. Chem. Soc.* 545 (1957).
[3] T. R. Govindachari, K. Nagarajan and P. C. Parthasarathy, *J. Chem. Soc.* 548 (1957).
[4] E. M. Bickoff, A. N. Booth, R. L. Lyman, A. L. Livingston, C. R. Thompson and F. De Eds, *Science* **126**, 969 (1957).
[5] E. M. Bickoff, A. L. Livingston and A. N. Booth, *Arch. Biochem. & Biophys.* **88**, 262 (1960).
[6] P. K. Grover and T. R. Seshadri, *Proc. Indian. Acad. Sci.* **38**, 122 (1953).

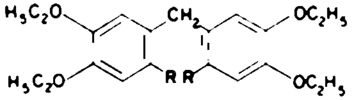
lithium aluminium hydride. One of the products isolated by decomposing the reaction mixture with dilute sulphuric acid was considered to be 3,4-diethoxy-6-hydroxybenzyl alcohol (IV). However, the benzoate of the compound on treatment with alkali and diethyl sulphate gave a product identical with 2,4,5:2′,4′,5′-hexaethoxydiphenylmethane (Vb), prepared from 2,4,5-triethoxybenzaldehyde by reduction with sodium borohydride followed by treatment with acid. Hence the reduction product should actually be 3,4,3′,4′-tetraethoxy-6,6′-dihydroxydiphenylmethane (Va) produced by the action of acid[7] on the initially formed alcohol (IV) during the process of isolation.



III



IV



V

a : R = OH

b : R = OC₂H₅

EXPERIMENTAL

Melting points are uncorrected. Ultra-violet absorption spectra were measured using a Beckmann Model DU Spectrophotometer.

4-Hydroxy-7-methoxy-3(o-methoxyphenyl)coumarin (Ia)

2-Hydroxy-4-methoxyphenyl *o*-methoxybenzyl ketone (2 g) in diethyl carbonate (25 ml) containing pulverized sodium (1·5 g) was warmed on a water-bath for 40 min. The granular sodium salt that separated was treated with a small volume of methanol to decompose excess sodium. Water (50 ml) was added, and the solution after repeated extraction with ether, made acidic to congo-red. The *coumarin* (1·8 g) separated out as a white solid, which on crystallization from methanol was obtained as colourless needles, m.p. 178°, λ_{max} 313 mμ (log ε 4·3) (Found: C, 68·6; H, 4·8. $C_{17}H_{14}O_5$ requires: C, 68·5; H, 4·7%).

The *acetate*, prepared by use of acetic anhydride and pyridine at 100° for 1/2 hr, formed colourless needles from acetic acid, m.p. 163° (Found: C, 67·5; H, 4·7. $C_{19}H_{16}O_6$ requires: C, 67·1; H, 4.7%).

The *methyl ether*, obtained by refluxing the coumarin (0·2 g) with methyl iodide (1 ml) and potassium carbonate (1 g) in dry acetone (5 ml) for 1 hr, had m.p. 119°, colourless cubes from aqueous methanol. (Found: C, 69·0; H, 5·1. $C_{18}H_{16}O_5$ requires: C, 69·2; H, 5·1%).

7′-Hydroxycoumarino(3′,4′:3,2)coumarone

The foregoing hydroxycoumarin (1 g) was heated with dry pyridine hydrochloride (8 g) at 220° in an atmosphere of nitrogen for 1 hr. The reaction mixture was then cooled and treated with water (20 ml). A brown semi-crystalline alkali-soluble mass separated on leaving in the ice-chest overnight. This was collected, washed with water and dried. After sublimation at 200°/1 mm and crystallization from methanol, *7′-hydroxycoumarino-(3′,4′:3,2)coumarone* (0·5 g) was obtained as needles, m.p. 285°, λ_{max} 240, 295, 330 mμ (log ε 4·15, 3·95, 4·32) (Found: C, 71·6; H, 3·4. ($C_{15}H_8O_4$ requires: C, 71·4; H, 3·2%).

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[7] T. R. Govindachari, K. Nagarajan and P. C. Parthasarathy, *J. Chem. Soc.* 912 (1958).

The *acetate*, prepared by use of acetic anhydride and pyridine in the cold, was obtained as needles, m.p. 105–106°, from acetic acid. (Found: C, 69·2; H, 3·4. $C_{17}H_{10}O_5$ requires: C, 69·4; H, 3·4%).

7′-Methoxycoumarino(3′,4′:3,2)*coumarone* (IIa)

The above hydroxylactone (0·5 g) was refluxed with methyl iodide (2 ml), actone (20 ml) and potassium carbonate (2 g) for 4 hr. After removal of acetone, water was added and the residue was washed with alcohol and then crystallized from acetic acid to yield colourless needles of *7′-methoxy coumarino*-(3′,4′:3,2)*coumarone* (0·3 g), m.p. 195–196°, λ_{max} 240, 295, 330 mμ (log ε 4·2, 3·95, 4·35) (Found: C, 72·2; H, 3·5. $C_{16}H_{10}O_4$ requires: C, 72·2; H, 3·8%).

5′,7′,6-Trimethoxycoumarino(3′,4′:3,2)*coumarone* (IIb)

2-Hydroxy-4,6-dimethoxyphenyl 2,4-dimethoxybenzyl ketone. 2,4,6-Trihydroxyphenyl 2,4-dimethoxybenzyl ketone (1 g), methyl sulphate (0·9 g), potassium carbonate (3 g) and acetone (25 ml) were heated on a water-bath for 5 hr. The residue (1 g), after evaporation of the solvent, yielded *the ketone* as colourless prisms from alcohol, m.p. 137–138° (Found: C, 65·3; H, 6·1. $C_{18}H_{20}O_6$ requires: C, 65·0; H, 6·0%).

4-Hydroxy-5,7-dimethoxy-3(*2,4-dimethoxyphenyl*)*coumarin* (Ib)

Cyclization of the above ketone (1 g) with diethyl carbonate (20 ml) and sodium dust (1 g) during 1 hr, gave the *coumarin* (0·8 g) which separated as needles from acetic acid, m.p. 227°, λ_{max} 317 mμ (log ε 4·22) (Found: C, 63·8; H, 5·2. $C_{19}H_{18}O_7$ requires: C, 63·7; H, 5·0%).

The *methyl ether* (0·1 g), prepared by the usual procedure, was obtained from aqueous alcohol as needles, m.p. 171° (Found: C, 64·7; H, 5·6. $C_{20}H_{20}O_7$ requires: C, 64·5; H, 5·4%).

5′,7′,6-Trimethoxycoumarino(3′,4′:3,2)*coumarone* (IIb)

The foregoing hydroxycoumarin (0·1 g) was heated with dry pyridine hydrochloride (3 g) at 250° in a current of nitrogen for ½ hr, cooled, and treated with water. The brown solid that separated was methylated with methyl iodide in the usual manner, to yield, *5′,7′,6-trimethoxycoumarino*(3′,4′:3,2) *coumarone* (50 mg), crystallizing in needles from acetic acid, m.p. 230°, λ_{max} 250, 345 mμ (log ε 4·27, 4·37) (Found: C, 66·2; H, 4·1. $C_{18}H_{14}O_6$ requires: C, 66·3; H, 4·3%).

2,4,5:2′,4′,5′-*Hexaethoxydiphenylmethane* (Vb)

The dibenzoate[8] (20 mg) was warmed on the water-bath with aqueous potassium hydroxide (1 g in 10 ml) for 1 hr, and to the resulting alkaline solution was added diethyl sulphate (1 ml) with shaking and warming. The reaction mixture was made distinctly alkaline to litmus and left overnight in the ice-chest. 2,4,5:2′,4′,5′-*Hexaethoxydiphenylmethane* separated out as needles from methanol, m.p. and mixed m.p. 93°, with an authentic specimen prepared as below:

2,4,5-Triethoxybenzaldehyde (0·5 g) in warm methanol (10 ml) was treated with sodium borohydride (0·2 g) with occasional shaking. Next morning, the reaction mixture was rendered acidic with dil 4 N HCl (20 ml) and the gummy material that separated solidified on digesting with alcohol to yield 2,4,5:2′,4′,5-*hexaethoxydiphenylmethane*, crystallizing in needles from alcohol, m.p. 93° (Found: C, 69·7; H, 8·4. $C_{25}H_{36}O_6$ requires; C, 69·4; H, 8·3%).

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