Reactions of Forskolin, a Biologically Active Diterpenoid from *Coleus forskohlii* [1]

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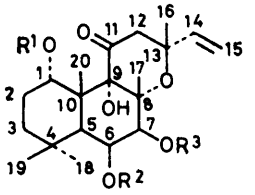
Forskolin (1) (7β-acetoxy-8,13-epoxy-1α,6β,9α-trihydroxylabd-14-en-11-one), the major diterpenoid of *Coleus forskohlii*, has potent positive inotropic, antihypertensive, and adenylate cyclase stimulant properties. The reactivity of its various functional groups (1α-OH, 6β-OH, the derived 7β-OH, 9α-OH, 11-oxo, and 14,15-double bond) has been studied through acylation, alkylation, dehydration, oxidation, and reduction reactions.

FORSKOLIN (1) (7β-acetoxy-8,13-epoxy-1α,6β,9α-trihydroxylabd-14-en-11-one) is the major diterpenoid from the Indian plant *Coleus forskohlii*.[2-4] It is of especial interest because of its potent positive inotropic, antihypertensive, and adenylate cyclase stimulant properties.[5-7]

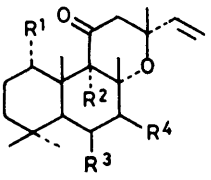
The molecule has been subjected to various chemical studies, first at the time of elucidation of its structure and later in work on the construction of analogues for the derivation of structure–activity relationships. In this paper, we describe mainly acylation, dehydration, oxidation, and reduction studies on forskolin and some of its derivatives.

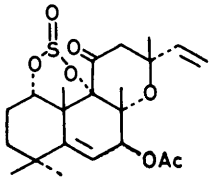


(1) $R^1 = R^2 = H$, $R^3 = Ac$
(2) $R^1 = R^3 = Ac$, $R^2 = H$
(3) $R^1 = R^2 = R^3 = Ac$
(4) $R^1 = R^3 = H$, $R^2 = Ac$
(5) $R^1 = H$, $R^2 = R^3 = Ac$
(6) $R^1 = R^2 = R^3 = H$
(7) $R^1 = R^2 = H$, $R^3 = COEt$
(8) $R^1 = Me$, $R^2 = R^3 = H$
(9) $R^1 = Me$, $R^2 = H$, $R^3 = Ac$

Forskolin gave the 1α-acetate (2) readily on treatment with acetic anhydride and pyridine at room temperature. Further acetylation, of the hindered 6β-OH group, to give the 1α,6β-diacetate (3) in low yield was only possible by heating at reflux for *ca.* 90 h. A better route to the 6-acyl derivatives involved utilisation of the proximal 7β-acyl group. On treatment with basic alumina in benzene, forskolin easily underwent acyl migration,[8] presumably through an ortho-ester intermediate, to give the 6β-acetyl-7-deacetyl derivative (4), which was then acetylated under controlled conditions to give either forskolin 6β-acetate (5) or forskolin 1α,6β,-diacetate (3). The preferential reactivity of the 7β-OH group was also demonstrated when 7-deacetylforskolin (6), obtained by hydrolysis of forskolin,[2] was reacylated under controlled conditions with propionic anhydride and pyridine to give the 7β-propionate (7). In contrast, in alkylation reactions of 7-deacetylforskolin, the preferential reactivity of the 7-OH group was not observed. The partial methylation of 7-deacetylforskolin gave the 1-methyl derivative (8), which on acetylation afforded 1-methylforskolin (9), identical with the product obtained by controlled methylation of forskolin.

Derivatisation of the 9α-OH group was achieved through treatment with phosgene–pyridine [9] and thionyl chloride–pyridine, giving the 1,9-carbonate (10) and 1,9-sulphite (11). When phosgene–pyridine was used with 7-deacetylforskolin, the 6β,7β-monocarbonate (12) and the 1α,9α:6β,7β-dicarbonate (13) were obtained.



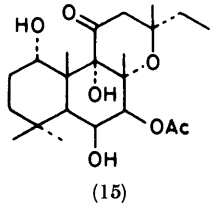


(10) $R^1R^2 = O{\cdot}CO{\cdot}O$, $R^3 = OH$, $R^4 = OAc$
(11) $R^1R^2 = O{\cdot}SO{\cdot}O$, $R^3 = OH$, $R^4 = OAc$
(12) $R^1 = R^2 = OH$, $R^3R^4 = O{\cdot}CO{\cdot}O$
(13) $R^1R^2 = R^3R^4 = O{\cdot}CO{\cdot}O$

(14)

The reaction of forskolin with thionyl chloride–pyridine also provided a dehydration product, the $\Delta^{5,6}$-1α,9α-sulphite (14).

Treatment of 14,15-dihydroforskolin (15) [2] with phosphorus pentachloride in benzene [10] caused smooth dehydration accompanied by methyl migration to yield the anhydro-derivative (16).



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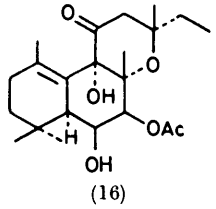
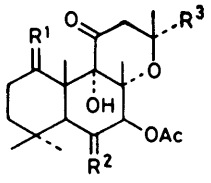
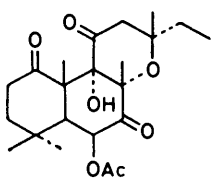


(16)

In oxidation studies, the susceptibilities of the hydroxy and vinyl groups were dependent on the reaction conditions. With Collins reagent,[11] forskolin gave 1-deoxy-1-oxoforskolin (17). With Jones [12] or Sarett's reagent,[13] the oxidation of 14,15-dihydroforskolin could be controlled to give either the ketone (18) or the dione (19). The mass spectrum of the 1-ketone (18) has the base peak at m/z 139 ($C_9H_{15}O$), a fragment typical of 1-oxo-steroids [14] (Scheme). The 1,7-dione (20) was



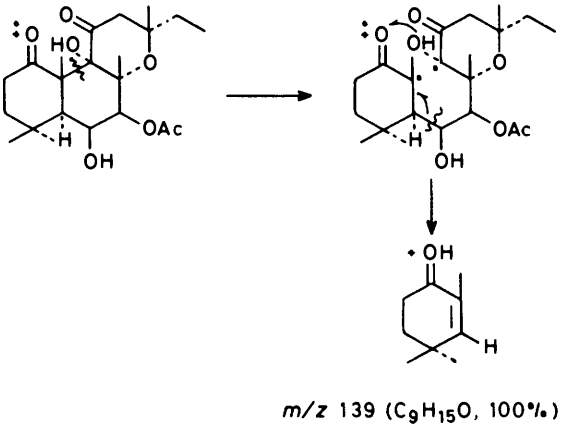
(17) R^1 = O, R^2 = H,OH, R^3 = $CH{:}CH_2$
(18) R^1 = O, R^2 = H,OH, R^3 = Et
(19) R^1 = R^2 = O, R^3 = Et



(20)

obtained by Jones oxidation of the 14,15-dihydro-derivative of (4).

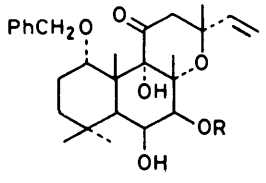
Periodic acid oxidation [15] was carried out on 1-benzyl-7-deacetylforskolin (22), obtained from forskolin



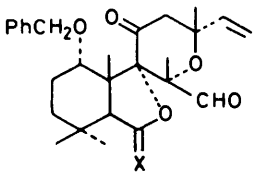
m/z 139 ($C_9H_{15}O$, 100%)

SCHEME

by benzylation and subsequent hydrolysis. Cleavage of the 6,7-glycol bond took place readily, to give the hemiacetal aldehyde (23), which on Sarrett oxidation provided the γ-lactone (24).

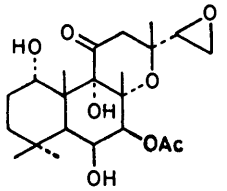


(21) R = Ac
(22) R = H



(23) X = H,OH
(24) X = O

Forskolin underwent smooth epoxidation by *m*-chloroperbenzoic acid [16] to give the 14,15-epoxide (25). On ozonolysis, the vinyl group of 1α,6β-diacetylforskolin (3) was cleaved to give the hemiacetal (26), which on acetylation formed the tetra-acetate (27).



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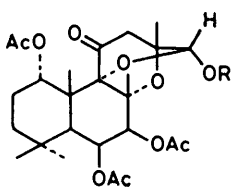
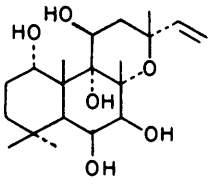


(26) R = H
(27) R = Ac

In reduction studies, the 11-oxo-group of forskolin as well as the generated oxo-functions in forskolin derivatives were stereospecifically reduced. With lithium aluminium hydride,[17] forskolin was reduced to the 11β-hydroxy-7-deacetyl derivative (28), while on reduction



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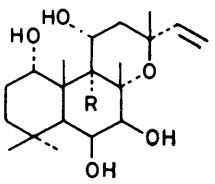
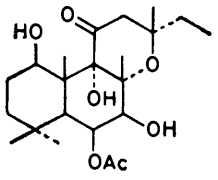


(29) R = OH
(30) R = H

with Na–EtOH [18] the 11α-hydroxy-7-deacetyl derivative (29) was obtained. In the latter reaction, the 9-dehydroxy-derivative (30) was also formed. With lithium tri-t-butoxyaluminium hydride,[19] the 1,7-dione (20) was reduced to the 1β-hydroxy-derivative (31).



(31)

The potential of the foregoing studies to provide analogues of forskolin for deriving structure–activity relationships is clear. Studies of this type will be described in a subsequent publication.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. U.v.–visible spectra were measured for methanolic solutions with a Carl Zeiss Specord spectrophotometer. I.r. spectra were determined with a Perkin-Elmer 157 spectrophotometer for KBr discs unless mentioned otherwise. ^{1}H N.m.r. spectra were measured for solutions in $CDCl_3$ with a Varian T-60 spectrometer (Me_4Si as internal standard). Mass spectra were recorded with an A.E.I. MS-9025 spectrometer. For column chromatography, the order of eluants used was hexane, hexane–benzene mixtures, benzene, benzene–ethyl acetate mixtures, and ethyl acetate. 'Usual work-up' refers to dilution with water followed by extraction with chloroform or ethyl acetate, washing the organic layer with water, drying over anhydrous sodium sulphate, and evaporating *in vacuo*. Light petroleum refers to the fraction of b.p. 60—80 °C.

1-*Acetylforskolin* (2).—A mixture of forskolin (1.0 g), pyridine (5 ml), and acetic anhydride (5 ml) was set aside overnight. The usual work-up gave 1-*acetylforskolin* (2) (0.8 g), m.p. 203—206 °C (from ethyl acetate–light petroleum); δ_H 2.0 and 2.16 (2 × 3 H, 2s, 2 OAc), 5.53 (2 H, d, *J* 4 Hz, 7α-H and overlapping 1β-H), and 4.46 (1 H, dd, *J* 4 and 3 Hz, 6α-H); $\nu_{max.}$ 3 500, 1 735, 1 710, and 1 640 cm^{-1} (Found: C, 63.5; H, 8.35. $C_{24}H_{36}O_8$ requires C, 63.7; H, 7.95%).

6-*Acetyl-7-deacetylforskolin* (4).—To a solution of forskolin

(1.0 g) in anhydrous benzene (100 ml), basic alumina (20.0 g) was added. The mixture was stirred for 120 h and filtered. The alumina was washed with ethyl acetate (100 ml). The benzene filtrate and the ethyl acetate washings were combined and evaporated to dryness under reduced pressure. The residue gave 6-*acetyl*-7-*deacetylforskolin* (4) (0.55 g), m.p. 208—210 °C (repeatedly from chloroform–light petroleum), δ_H 5.86 (1 H, dd, *J* 4 and 3 Hz, 6α-H), 4.66 (1 H, br, s, $W_{\frac{1}{2}}$ 7 Hz, 1β-H), and 4.30 (1 H, d, *J* 4 Hz, 7α-H); $\nu_{max.}$ 3 400, 3 200, 1 725, and 1 700 cm^{-1} (Found: C, 64.1; H, 8.5. $C_{22}H_{34}O_7$ requires C, 64.4; H, 8.3%).

1,6-*Diacetylforskolin* (3).—A mixture of 6-acetyl-7-deacetylforskolin (4) (0.2 g), pyridine (2 ml), and acetic anhydride (2 ml) was set aside overnight. The usual work-up gave 1,6-diacetylforskolin (3) (0.17 g), m.p. 216—218 °C (from ethyl acetate–light petroleum); δ_H 5.56 (3 H, m, $W_{\frac{1}{2}}$ 7 Hz, 1β-H, 6α-H, 7α-H), 2.10 (3 H, s, OAc), and 2.03 (6 H, s, 2 OAc); $\nu_{max.}$ 3 420, 1 750, 1 730, 1 720, and 1 640 cm^{-1} (Found: C, 63.45; H, 8.15. $C_{26}H_{38}O_9$ requires C, 63.15; H, 7.7%).

6-*Acetylforskolin* (5).—To a cooled solution (0—5 °C) of 6-acetyl-7-deacetylforskolin (4) (0.20 g) in pyridine (2 ml), acetic anhydride (2 ml) was added. The mixture was stirred for 3 h at 0—5 °C and 0.5 h at room temperature. The usual work-up gave a gum which was chromatographed over silica gel. The fractions eluted in benzene–ethyl acetate (9 : 1) gave 6-*acetylforskolin* (5) (0.078 g), m.p. 299—301 °C (from ethyl acetate), δ_H[($^2H_5$)pyridine] 6.15 (2 H, br, s, $W_{\frac{1}{2}}$ 4 Hz, 6α-H and 7α-H), 5.00 (1 H, br, s, $W_{\frac{1}{2}}$ 4 Hz, 1β-H), 2.08 (3 H, s, OAc), and 1.93 (3 H, s, OAc); $\nu_{max.}$ 3 400, 1 735, and 1 720 cm^{-1} (Found: C, 63.4; H, 7.7. $C_{24}H_{36}O_8$ requires C, 63.7; H, 7.95%).

7-*Deacetyl*-7-*propionylforskolin* (7).—To a solution of 7-deacetylforskolin (6) [2] (1.0 g) in pyridine (5 ml), propionic anhydride (5 ml) was added at 0 °C and the reaction was carried out as for the preparation of (5) to give 7-*deacetyl*-7-*propionylforskolin* (7) (0.7 g), m.p. 175—197 °C (from ethyl acetate–light petroleum); δ_H 5.50 (1 H, d, *J* 4 Hz, 7α-H), 5.0 (2 H, m, 1β-H, 6α-H), and 2.40 and 1.35 (2 H, and 3 H, q and t, respectively, O_2CEt); $\nu_{max.}$ 3 500, 1 735, 1 710, and 1 640 cm^{-1} (Found: C, 64.9; H, 8.25. $C_{23}H_{36}O_7$ requires C, 65.1; H, 8.5%).

1-O-*Methyl*-7-*deacetylforskolin* (8).—7-Deacetylforskolin (6) (0.50 g), acetone (50 ml), dimethyl sulphate (0.19 g), and anhydrous potassium carbonate (5 g) were refluxed for 10 h. The acetone was decanted and the potassium carbonate cake washed thoroughly with acetone. The combined acetone solutions were concentrated *in vacuo* to obtain an oil. The product was chromatographed on silica gel (10 g); elution with benzene–ethyl acetate (95 : 5) gave 1-O-*methyl*-7-*deacetylforskolin* (8) as an oil (0.37 g); δ_H 3.23 (3 H, s, OCH_3), 4.13 (1 H, d, *J* 4 Hz, 7α-H), and 4.41 (1 H, br, t, 1β-H); $\nu_{max.}$ 3 500—3 300, 1 730, and 1 645 cm^{-1} (Found: C, 65.8; H, 8.85. $C_{21}H_{34}O_6$ requires C, 65.95; H, 8.9%).

1-*O*-*Methylforskolin* (9).—(a) *From* 1-O-*methyl*-7-*deacetylforskolin* (8). A mixture of 1-*O*-methyl-7-deacetylforskolin (8) (0.5 g), pyridine (2.0 ml), and acetic anhydride (2 ml) was set aside overnight. The usual work-up gave 1-O-*methylforskolin* (9) (0.43 g), m.p. 193—194 °C (from ethyl acetate–light petroleum); δ_H 3.23 (3 H, s, OCH_3), 4.45 (1 H, m, $W_{\frac{1}{2}}$ 10 Hz, 1β-H), and 5.51 (1 H, d, *J* 4 Hz, 7α-H); $\nu_{max.}$ 3 250, 1 750, 1 730, and 1 645 cm^{-1} (Found: C, 64.9; H, 8.15. $C_{23}H_{36}O_7$ requires C, 65.1; H, 8.5%).

(b) *From forskolin* (1). Forskolin (1) (0.5 g) was methylated with dimethyl sulphate (0.20 g) in acetone (50 ml) and potassium carbonate (5 g) as for the preparation of (8). The crude product was chromatographed over silica gel (10 g); elution with benzene–ethyl acetate (98 : 2) gave 1-*O*-methylforskolin (9) (0.38 g), m.p. 192—193 °C (from ethyl acetate–light petroleum), identical with the product from experiment (a).

Forskolin 1,9-*Carbonate* (10).—To a solution of forskolin (1.5 g) in pyridine (3 ml), a solution of phosgene in toluene (3 ml) was added at 0 °C. The mixture was stirred at the same temperature for 1 h. After the usual work-up the residue gave *forskolin* 1,9-*carbonate* (10) (1.22 g), m.p. 182—184 °C (from ethyl acetate–light petroleum); δ_H 5.40 (1 H, d, *J* 4 Hz, 7α-H), 4.90 (1 H, br, s, $W_{\frac{1}{2}}$ 6 Hz, 1β-H), and 4.56 (1 H, dd, *J* 4 and 3 Hz, 6α-H); $\nu_{max.}$ 3 500, 1 750, 1 725, and 1 640 cm^{-1} (Found: C, 63.7; H, 7.45. $C_{23}H_{32}O_8$ requires C, 63.3; H, 7.35%).

The 1,9:6,7-*Dicarbonate* (13) *and the* 6,7-*Carbonate* (12).—7-Deacetylforskolin (6) [2] (1.5 g) in pyridine (3 ml) was treated with phosgene as for the preparation of (10). The crude product was chromatographed over silica gel. Elution with benzene–ethyl acetate (97 : 3) gave the 1,9:6,7-dicarbonate (13) (0.47 g), m.p. 281—283 °C (from chloroform–light petroleum); δ_H 5.15 (1 H, d, *J* 4 Hz, 7α-H) and 5.0 (2 H, m, 1β-H and 6α-H); $\nu_{max.}$ 3 450, 1 850, 1 770, 1 740, and 1 635 cm^{-1} (Found: C, 63.2; H, 6.6. $C_{22}H_{28}O_8$ requires C, 62.85; H, 6.65%). The fractions eluted with benzene–ethyl acetate (94 : 6) gave the 6,7-*monocarbonate* (12) (0.025 g), m.p. 218—222 °C; δ_H 5.05 (2 H, m, 6α-H and 7α-H), and 4.60 (1 H, br, s, $W_{\frac{1}{2}}$ 6 Hz, 1β-H); $\nu_{max.}$ 3 450, 1 825, 1 775, 1 740, and 1 640 cm^{-1} (Found: C, 63.7; H, 8.0. $C_{21}H_{30}O_7$ requires C, 63.95; H, 7.6%).

5,6-*Didehydro*-6-*deoxyforskolin* 1,9-*Sulphite* (14) *and Forskolin* 1,9-*Sulphite* (11).—To a solution of forskolin (1.0 g) in pyridine (10.0 ml) at 0—5 °C was added thionyl chloride (1.0 ml). The mixture was stirred at the same temperature for 10 min and poured into ice–water. After the usual work-up, the crude product was chromatographed over silica gel; the fractions eluted in benzene gave 5,6-*didehydro*-6-*deoxyforskolin* 1,9-*sulphite* (14) (0.25 g), m.p. 194—195 °C (from ethyl acetate–light petroleum); δ_H 5.88 (1 H, d, *J* 2 Hz, 7α-H), 5.42 (1 H, d, *J* 2 Hz, 6α-H), and 5.19 (1 H, br, s, $W_{\frac{1}{2}}$ 6 Hz, 1β-H); $\nu_{max.}$ 1 770—1 720br, 1 655, and 1 635 cm^{-1} (Found: C, 60.1; H, 7.1; S, 7.0. $C_{22}H_{30}O_7S$ requires C, 60.25; H, 6.85; S, 7.3%). The fractions eluted in benzene–ethyl acetate (95 : 5) gave the 1,9-sulphite (11) (0.2 g), m.p. 211—216 °C (from benzene–light petroleum); δ_H 5.36 (1 H, d, *J* 4 Hz, 7α-H), 5.05 (1 H, br, s, $W_{\frac{1}{2}}$ 6 Hz, 1β-H), and 4.46 (1 H, dd, *J* 4 and 3 Hz, 6α-H); $\nu_{max.}$ 3 420, 1 735, 1 710, and 1 640 cm^{-1}; M^+ 456.182 (Found: C, 58.0; H, 7.5; S, 7.3. $C_{22}H_{32}O_8S$ requires C, 57.9; H, 7.0; S, 7.0%).

10-*Demethyl*-1,2-*didehydro*-1-*deoxy*-14,15-*dihydro*-1-*methylforskolin* (16).—To a cooled (0—5 °C) solution of 14,15-dihydroforskolin (15) [2] (1.25 g) in benzene (24 ml), phosphorous pentachloride (1.0 g) was added with stirring. The mixture was brought to room temperature and stirred for a total of 15 min, and the excess of phosphorus pentachloride was decomposed with ice. The usual work-up gave the anhydro-derivative (16) (0.67 g), m.p. 173—176 °C (from ethyl acetate–light petroleum); δ_H 5.16 (1 H, d, *J* 4 Hz, 7α-H), 4.43 (1 H, dd, *J* 4 and 3 Hz, 6α-H), and 1.84 (3 H, s, CH_3C=); $\nu_{max.}$ 3 400, 1 725br, and 1 655 cm^{-1}; M^+ 394.235 (Found: C, 66.45; H, 8.15. $C_{22}H_{34}O_6$ requires C, 67.0; H, 8.65%).

1-*Deoxy*-1-*oxoforskolin* (17).—To a stirred suspension of

Collins reagent (2.1 g) in methylene chloride (45 ml) was added a solution of forskolin (1.5 g) in methylene chloride (60 ml). The mixture was stirred for 2.5 h and filtered. The residue was washed with methylene chloride (50 ml) and the combined methylene chloride filtrates were washed with N-hydrochloric acid, saturated aqueous sodium hydrogencarbonate, and water, dried, and evaporated to dryness. The residue gave 1-*deoxy*-1-*oxoforskolin* (17) (1.2 g), m.p. 202—204 °C (from ethyl acetate–light petroleum); δ_H 5.40 (1 H, d, *J* 4 Hz, 7α-H), 4.40 (1 H, dd, *J* 4 and 3 Hz, 6α-H), and 3.10 (1 H, m, 2β-H); $\nu_{max.}$ 3 500, 1 725, 1 710, and 1 650 cm^{-1} (Found: C, 65.05; H, 8.25. $C_{22}H_{32}O_7$ requires C, 64.7; H, 7.85%).

14,15-*Dihydro*-1-*deoxy*-1-*oxoforskolin* (18).—To a solution of 14,15-dihydroforskolin (15) [2] (1.50 g) in acetone (10 ml) at 0—5 °C was added Jones reagent (1.0 ml) dropwise with stirring. The mixture was stirred at 0—5 °C for 15 min. The excess of reagent was decomposed with methanol and the solvents were removed. The usual work-up gave 14,15-*dihydro*-1-*deoxy*-1-*oxoforskolin* (18) (0.7 g), m.p. 230—233 °C (from ethyl acetate–light petroleum); δ_H 5.30 (1 H, d, *J* 4 Hz, 7α-H), 4.34 (1 H, dd, *J* 4 and 3 Hz, 6α-H), and 3.03 (1 H, dd, *J* 7 and 6 Hz, 2β-H); $\nu_{max.}$ 3 450, 1 710, and 1 700 cm^{-1} (Found: C, 64.2; H, 8.15. $C_{22}H_{34}O_7$ requires C, 64.4; H, 8.3%).

14,15-*Dihydro*-1,6-*dideoxy*-1,6-*dioxoforskolin* (19).—14,15-Dihydroforskolin (15) [2] (1.8 g) was oxidised using Jones reagent as described for the preparation of (18), except that the reaction mixture was further stirred at room temperature for 45 min. The excess of reagent was decomposed with methanol and the solvents were removed. The usual work-up gave 14,15-*dihydro*-1,6-*dideoxy*-1,6-*dioxoforskolin* (19) (1.1 g), m.p. 163—165 °C (from ethyl acetate–light petroleum); δ_H 5.61 (1 H, s, 7α-H), 3.50 (1 H, s, 5α-H), and 3.0 (1 H, br, m, 2β-H); $\nu_{max.}$ 3 400, 1 750, 1 730, and 1 710 cm^{-1} (Found: C, 64.4; H, 7.85. $C_{22}H_{30}O_7$ requires C, 65.0; H, 7.4%).

6-*Acetyl*-7-*deacetyl*-1,7-*dideoxy*-1,7-*dioxo*-14,15-*dihydroforskolin* (20).—A solution of 6-acetyl-7-deacetylforskolin (4) (2.0 g) in ethyl acetate (100 ml) was hydrogenated over Pd–C (5%; 0.5 g) for ½ h. The solution was filtered and the filtrate was evaporated to dryness to give the 14,15-*dihydro-derivative* (1.8 g), m.p. 209—212 °C (from ethyl acetate–light petroleum) (Found: C, 64.2; H, 8.5. $C_{22}H_{36}O_7$ requires C, 64.1; H, 8.75%), which was oxidised with Jones reagent as for the preparation of (19) to give the *derivative* (20) (1.1 g), m.p. 137—138 °C (from ethyl acetate–light petroleum); δ_H 5.43 (d, *J* 3 Hz, 6α-H); $\nu_{max.}$ 3 400, 1 750, 1 730, and 1 710 cm^{-1} (Found: C, 64.3; H, 7.5. $C_{22}H_{32}O_7$ requires C, 64.7; H, 7.85%).

1-*Benzylforskolin* (21).—A mixture of forskolin (1.0 g), benzyl bromide (1.3 ml), anhydrous potassium iodide (1.0 g), anhydrous potassium carbonate (5.0 g), and dry acetone (30 ml) was refluxed for 17 h and filtered. The filtrate was evaporated to dryness and the residue after usual work-up was chromatographed over silica gel. The fractions eluted with benzene–ethyl acetate (95 : 5) gave 1-*benzylforskolin* (21) (0.9 g), m.p. 132—134 °C (from ethyl acetate–light petroleum); δ_H 7.31 (5 H, br, s, C_6H_5) and 4.44 (2 H, m, OCH_2Ph); $\nu_{max.}$ 3 500, 3 200, 1 725, 1 710, and 1 645 cm^{-1} (Found: C, 69.3; H, 8.15. $C_{29}H_{40}O_7$ requires C, 69.6; H, 8.0%).

1-*Benzyl*-7-*deacetylforskolin* (22).—A mixture of 1-benzylforskolin (21) (1.4 g) in aqueous methanol (80%; 50 ml) and sodium hydroxide (0.2 g) was stirred at room temperature for 1 h. The solvents were removed *in vacuo* and the residue after usual work-up gave 1-*benzyl*-7-*deacetylforskolin* (22) (0.95 g), m.p. 80—85 °C (from ethyl acetate–light petroleum); δ_H 7.27 (5 H, br, s, C_6H_5), 4.40 (2 H, m, OCH_2-Ph), and 4.13 (1 H, d, *J* 4 Hz, 7α-H); $\nu_{max.}$ 3 450, 3 250, 1 775, and 1 640 cm^{-1} (Found: C, 71.15; H, 8.65. $C_{27}H_{38}O_6$ requires C, 70.75; H, 8.3%).

The Hemiacetal Aldehyde (23).—To a solution of 1-benzyl-7-deacetylforskolin (22) (0.125 g) in aqueous methanol (15 ml) was added periodic acid (0.25 g), and the mixture was stirred for 2 h at room temperature. The solvents were removed and the residue after usual work-up gave the 6,7-*seco-hemiacetal aldehyde* (23) (0.085 g), a gum (resisted crystallisation); δ_H 9.48 (1 H, s, CHO), 7.26 (5 H, m, C_6H_5), and 4.71 and 4.26 (2 H, 2d, *J* 12 Hz each, OCH_2Ph); $\nu_{max.}$ ($CHCl_3$) 3 460, 3 220, 1 730, and 1 715 cm^{-1} (Found: C, 70.65; H, 7.65. $C_{27}H_{36}O_6$ requires C, 71.05; H, 7.9%).

The γ-Lactone (24).—To a solution of chromic acid (1 g) in pyridine (2 ml), the hemiacetal aldehyde (23) (0.1 g) was added, and the mixture was stirred at room temperature for 3 h and kept overnight. The usual work-up gave the *γ-lactone* (24) (0.042 g), m.p. 159—162 °C (from ethyl acetate–light petroleum); δ_H 9.45 (1 H, s, CHO), 7.30 (5 H, m, C_6H_5), 4.75 and 4.21 (2 H, 2d, *J* 12 Hz each, OCH_2Ph), 3.83 (1 H, br, s, $W_{\frac{1}{2}}$ 7 Hz, 1β-H), and 3.53 (1 H, s, 5α-H); $\nu_{max.}$ ($CHCl_3$) 1 775, 1 735, 1 730, and 1 645 cm^{-1}; M^+ 454.235 (Found: C, 71.15; H, 7.35. $C_{27}H_{34}O_6$ requires C, 71.35; H, 7.5%).

Forskolin 14,15-*Epoxide* (25).—To a cooled solution (0—5 °C) of forskolin (0.4 g) in chloroform (25 ml) was added *m*-chloroperbenzoic acid (0.8 g) and the mixture was set aside overnight at 0 °C. The usual work-up gave *forskolin epoxide* (25) (0.31 g), m.p. 155—156 °C (from ethyl acetate–light petroleum); δ_H 5.28 (1 H, d, *J* 4 Hz, 7β-H), 4.48 (2 H, m, 1β-H, and 6α-H), and 2.80—3.40 (3 H, m, oxiran); $\nu_{max.}$ 3 450, 3 250, 1 735, 1 720, and 1 640 cm^{-1} (Found: C, 62.1; H, 8.25. $C_{22}H_{34}O_8$ requires C, 61.95; H, 8.0%).

The Hemiacetal (26).—Through a solution of 1,6-diacetylforskolin (3) (1.0 g) in chloroform (150 ml), ozonised oxygen was passed for ½ h at 0 °C. The solution was diluted with water (10 ml), zinc dust (0.50 g) was added, and the mixture was stirred at room temperature for 1 h. The usual work-up gave the *hemiacetal* (26) (0.75 g), m.p. 279—280 °C (from ethyl acetate–light petroleum); δ_H 5.80 (1 H, dd, *J* 4 and 3 Hz, 6α-H), 5.53 (1 H, br, s, $W_{\frac{1}{2}}$ 7 Hz, 1β-H), 5.31 (1 H, d, *J* 4 Hz, 7α-H), 5.15 (1 H, s, 14-H), 2.10 (3 H, s, OAc), and 2.05 (6 H, s, 2 OAc); $\nu_{max.}$ 3 500 and 1 735br cm^{-1} (Found: C, 60.1; H, 6.95. $C_{25}H_{36}O_{10}$ requires C, 60.5; H, 7.25%).

The Hemiacetal Acetate (27).—The hemiacetal (26) (0.10 g) was acetylated at room temperature with acetic anhydride and pyridine to give the *acetate* (27) (0.09 g), m.p. 217—218 °C (from ethyl acetate–light petroleum), δ_H 6.18 (1 H, s, 14-H), 5.80 (1 H, dd, *J* 4 and 3 Hz, 6α-H), 5.55 (1 H, br, s, $W_{\frac{1}{2}}$ 7 Hz, 1β-H), 5.31 (1 H, d, *J* 4 Hz, 7α-H), 2.06 (2 H, s, 2 OAc), 2.03 (3 H, s, OAc), and 1.91 (3 H, s, OAc); $\nu_{max.}$ 1 735br cm^{-1} (Found: C, 60.5; H, 7.65. $C_{27}H_{38}O_{11}$ requires C, 60.2; H, 7.05%).

8,13-*Epoxy*-1α,6β,7β,9α,11β-*pentahydroxylabd*-14-*ene* (28).—To a cooled (0—5 °C) and stirred solution of forskolin (1.0 g) in dry ether was added lithium aluminium hydride (0.5 g) and the mixture was refluxed for 4 h. The excess of reagent was decomposed with ethyl acetate (5 ml) followed by aqueous ethyl acetate (4 ml). The usual work-up gave the *derivative* (28) (0.53 g), m.p. 205—209 °C (from ethyl acetate–benzene); δ_H 4.40 (2 H, m, 1β-H and 6α-H), 4.05

(2 H, br, t, $W_{\frac{1}{2}}$ 7 Hz, 11α-H), and 3.85 (d, J 4 Hz, 7α-H); $\nu_{max.}$ 3 350 and 1 630 cm^{-1} (Found: C, 64.3; H, 9.4. $C_{20}H_{34}O_6$ requires C, 64.85; H, 9.2%).

8,13-*Epoxy*-1α,6β,7β,9α,11α-*pentahydroxylabd*-14-*ene* (29) *and* 8,13-*Epoxy*-1α,6β,7β,11α-*tetrahydroxylabd*-14-*ene* (30).—To a stirred solution of forskolin (1.0 g) in dry ethanol (60 ml) were added sodium pieces (3.0 g) during 45 min. The stirring was continued for 2 h at room temperature, then the mixture was refluxed for 45 min, cooled, acidified with hydrochloric acid, and filtered. The filtrate was concentrated *in vacuo* and the residue after the usual work-up was chromatographed over silica gel. The fractions eluted with benzene–ethyl acetate (85 : 15) gave the *derivative* (30) (0.45 g), 180—181 °C (from ethyl acetate–light petroleum); δ_H 4.26 (1 H, dd, J 4 and 3 Hz, 6α-H), 3.43 (2 H, m, $W_{\frac{1}{2}}$ 7 Hz, 1β-H and 7α-H), and 4.05 (1 H, m, $W_{\frac{1}{2}}$ 18 Hz, 11β-H); $\nu_{max.}$ 3 450 and 1 640 cm^{-1}; M^+ 354.0 (Found: C, 67.8; H, 9.85. $C_{20}H_{34}O_5$ requires C, 67.8; H, 9.6%). The fractions eluted with benzene–ethyl acetate (60 : 40) gave the *derivative* (29), m.p. 176—179 °C (from ethyl acetate–light petroleum); δ_H 4.18 (1 H, dd, J 4 and 3 Hz, 6α-H), and 3.90 and 3.63 (3 H, 2m, $W_{\frac{1}{2}}$ 14 and 4 Hz, 11β-H, 1β-H, and 7α-H); $\nu_{max.}$ 3 450 and 1 640 cm^{-1} (Found: C, 64.85; H, 9.2. $C_{20}H_{34}O_6$ requires C, 64.85; H, 9.2%).

6β-*Acetoxy*-8,13-*epoxy*-1β,7β,9α-*trihydroxylabdan*-11-*one* (31).—To a cooled (0—5 °C), stirred slurry of lithium-tri-t-butoxyaluminium hydride (prepared from 0.38 g of lithium aluminium hydride) in dry ether (15 ml) was added dropwise a solution of the derivative (20) (0.20 g) in dry ether (10 ml), and stirring was continued at the same temperature for 1 h. The mixture was processed as in the preparation of (28). The product was chromatographed over silica gel; elution with light petroleum–ethyl acetate (70 : 30) gave the *derivative* (31) (0.076 g), m.p. 206—207 °C (from ethyl acetate–light petroleum); δ_H 5.73 (1 H, dd, J 4 and 3 Hz, 6α-H), 3.92 (1 H, dd, J 8 and 12 Hz, 1α-H), and 3.85 (d, J 4 Hz 7α-H); $\nu_{max.}$ 3 375, 3 500, 1 735, and 1 700 cm^{-1}; M^+ 412 (Found: C, 64.35; H, 9.15. $C_{22}H_{36}O_7$ requires C, 64.1; H, 8.75%).

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