Tetrahedron Vol. 41, No. 12, pp. 2479 to 2482, 1985
Printed in Great Britain.

0040-4020/85 $3.00+.00
Pergamon Press Ltd.

SYNTHESIS OF ERYTHRININ A, A NATURALLY OCCURRING PYRANOISOFLAVONE

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(*Received in UK* 15 *January* 1985)

Abstract - Erythrinin A (10) has been synthesised by the oxidative rearrangement of dihydropyranochalcone 1 with thallium(III) nitrate (TTN) in trimethyl orthoformate (TMOF) to the dimethyl acetal 2, followed by cyclisation to 3, demethylation to 6 and dehydrogenation. Compound 10 could also be obtained from chalcone 4 on similar rearrangement followed by cyclisation, demethoxymethylation and dehydrogenation. In another route, chalcone 7 was oxidatively rearranged with TTN in TMOF, to 8 which on treatment with HCl yielded 10.

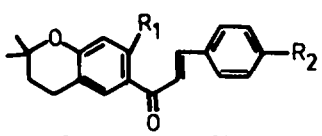
Erthrinin A, a naturally occurring pyranoisoflavone was isolated by Deshpande et al[1] from the bark of Erythrina variegata Linn. and assigned structure 10 on the basis of elemental analysis and spectral data. In this paper, we report the synthesis of 10 by the TTN mediated oxidative rearrangement of appropriate chalcones. Farkas et al[2] synthesised some simple isoflavones by the rearrangement of chalcones with TTN in methanol. The water of crystallisation present in TTN reacts with the solvent system and the acetals, resulting in the formation of complex mixtures of products. TTN readily dissolves in TMOF and the resultant solution contains water free TTN. Hence oxidations with TTN-TMOF are much faster than those with TTN-MeOH and result in excellent yields of the products[3]. In the present study, TTN-TMOF was used to bring about the rearrangement of chalcones 1, 4 and 7.

RESULTS AND DISCUSSION

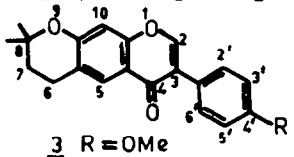
Dihydropyranochalcone 1 was treated with TTN in TMOF to give the dimethylacetal 2 which underwent cyclisation in presence of HCl to give dihydroerythrinin A methyl ether 3. Demethylation of 3 with HBr gave dihydroerythrinin A (6). The IR spectrum of 6 showed absorption at 3350 cm^{-1} (free hydroxyl) and the PMR spectrum showed the presence of two two-proton doublets in AA'BB' pattern with the C_3,-H and C_5,-H doublet centering at δ 7.00 (J = 8 Hz) and C_2,-H and C_6,-H doublet centering at δ 7.48 (J = 8 Hz). A singlet at 8.72 due to the C_4,-OH disappeared on D_2O exchange. Protection of a phenolic hydroxyl by methoxymethylation has the advantage that demethoxymethylation can be brought about under milder conditions than demethylation. With this in view, chalcone 4 was prepared by condensation of 6-acetyl-7-hydroxy-2,2-dimethylchroman and 4-methoxymethoxybenzaldehyde in presence of alkali. This chalcone on oxidation with TTN in TMOF gave the dimethylacetal 5 which on treatment with methanolic HCl underwent both cyclisation and demethoxymethylation to give 6, identical with

the demethylated product from 3. Dehydrogenation of 3 and 6 with DDQ in benzene gave erythrinin A methyl ether (9) and erythrinin A (10) respectively.

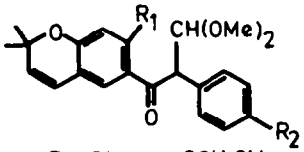
In an alternative route to 10, 6-acetyl-7-hydroxy-2,2-dimethylchromene was condensed with 4-methoxymethoxybenzaldehyde to give chalcone 7. This on oxidation with TTN in TMOF followed by treatment with acid gave 10 identical



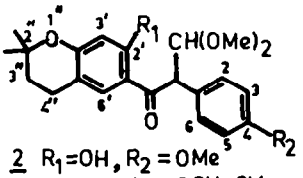
1 R_1=OH, R_2 =OMe
4 R_1=OH, R_2 =OCH_2OMe



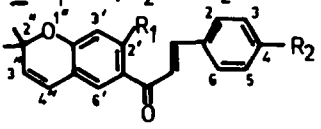
3 R =OMe
6 R = OH



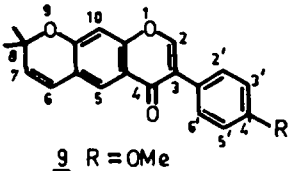
8 R_1=OH, R_2=OCH_2OMe



2 R_1=OH, R_2 = OMe
5 R_1=OH, R_2 =OCH_2OMe



7 R_1=OH, R_2 =OCH_2OMe



9 R =OMe
10 R =OH

with the dehydrogenation product from 6. The biosynthesis of isoflavones from chalcones has been shown to involve a 1,2-aryl migration and the present synthesis of erythrinin A represents a laboratory analogy of the biogenetic route.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 237 spectrometer and PMR spectra in $CDCl_3$ on a Varian XL-100 spectrometer (100 MHz) using TMS as internal standard.

Rearrangement of chalcone 1 with TTN and acid cyclisation of 2.

Synthesis of 3-(4'-methoxy)phenyl-8,8-dimethyl-6,7-dihydro-4H,8H-benzo(1,2-b:5,4-b')dipyran-4-one (3). To a solution of chalcone 1[4] (300 mg) in methanol (30 ml) a solution TTN (400 mg) in TMOF (6 ml) was added in portions and the mixture stirred for 1 h. The solution of the acetal 2 thus obtained was filtered from the inorganic salts and directly refluxed with HCl (10%, 5 ml) for 4 h. Removal of the solvent gave a residue which was extracted with chloroform, washed with sodium bicarbonate and water and dried. The product obtained on removal of solvent crystallised from ethanol to give 3 as colourless plates (110 mg), m.p. 183-84° ; PMR : δ 1.42(s,6H, $(CH_3)_2C<$), 1.90(t,2H,7-CH_2,J=7Hz), 2.94(t,2H,6-CH_2,J=7Hz), 3.88(s,3H,C_4'-OCH_3), 6.82(s,1H,C_{10}-H), 7.00(d,2H, C_3'-H and C_5'-H, J=8Hz), 7.52(d,2H,C_2'-H and C_6'-H,J=8Hz), 7.90(s,1H,C_5-H), 8.04(s,1H,C_2-H) (Found : C, 74.7 ; H, 5.8. $C_{21}H_{20}O_4$ requires C, 75.0 ; H, 6.0%).

Demethylation of dihydroerythrinin A methyl ether (3)

Formation of 3-(4'-hydroxy)phenyl-8,8-dimethyl-6,7-dihydro-4H,8H-benzo(1,2-b:5,4-b')dipyran-4-one (6). To a solution of 3 (60 mg) in acetic anhydride (6 ml), HBr (48%, 2 ml) was added in drops, the mixture heated on a water bath for 6 h, cooled and poured into ice-cold water. The resulting solid was air-dired and purified by passing through a silica gel column and eluting

with benzene-ethyl acetate (90:10). The product crystallised from dilute methanol as light grey plates (20 mg), m.p. 283-85° (decomp) ; IR : 3350, 1630 cm^{-1}; PMR : δ 1.44(s,6H,$(CH_3)_2C<$), 1.94(t,2H,7-CH_2,J=8Hz), 2.90(t,2H, 6-CH_2,J=8Hz), 6.84(s,1H,C_{10}-H), 7.00(d,2H,C_3,-H and C_5,-H,J=8Hz), 7.48(d,2H, C_2,-H and C_6,-H,J=8Hz), 7.88(s,1H,C_5-H), 8.16(s,1H,C_2-H), 8.72(s,1H,C_4,-OH,D_2O exchangeable). (Found : C, 74.1 ; H, 5.7. $C_{20}H_{18}O_4$ requires C, 74.5 ; H,5.6%).

Condensation of 6-acetyl-7-hydroxy-2,2-dimethylchroman with 4-methoxy methoxybenzaldehyde

Formation of 2'-hydroxy-4-methoxymethoxy-3'',4''-dihydro-2'',2''-dimethyl-2H-pyrano(4',5':6'',5'')chalcone (4). A solution of 6-acetyl-7-hydroxy-2,2-dimethylchroman[5] (250 mg) in ethanol (20 ml) was stirred with 4-methoxymethoxybenzaldehyde (230 mg) and aqueous KOH (30%, 10 ml) at room temperature for 36 h and the mixture was poured into ice-water mixture. The solid formed on neutralisation with dilute HCl was washed with water and crystallised from ethanol to give 4 as yellow plates (200 mg), m.p. 130-31° (Found : C, 71.4 ; H, 6.7. $C_{22}H_{24}O_5$ requires C, 71.7 ; H, 6.5%).

Rearrangement of chalcone 4 with TTN and acid cyclisation of 5

Synthesis of 3(4'-hydroxy)phenyl-8,8-dimethyl-6,7-dihydro-4H,8H-benzo(1,2-b:5,4-b') dipyran-4-one (6). Chalcone 4 (150 mg) was dissolved in methanol(20 ml) and to it was added in portions a solution of TTN (300 mg) in TMOF (5 ml). The mixture was stirred for 1 h and the inorganic salts were filtered off. The solution containing the acetal 5 was refluxed with HCl (10%, 4 ml) for 4 h and worked up. The product after purification crystallised from dilute methanol as light grey plates (80 mg), m.p. 284-85°(decomp).

Dehydrogenation of dihydroerythrinin A methyl ether (3) and dihydroerythrinin A (6)

To a solution of 3 or 6 (60 mg) in dry benzene (20 ml), DDQ (120 mg) was added and the mixture was refluxed for 30 h, cooled and the hydroquinone filtered off.

(i) Erythrinin A methyl ether (9). Removal of solvent gave a residue which after purification in a silica gel column by elution with hexane-ethyl acetate (98:2) crystallised from the same solvent mixture as colourless plates (35 mg), m.p. 139-41° ; IR : 1635, 1610, 1590, 1575 cm^{-1}; PMR : δ 1.54(s,6H,$(CH_3)_2C<$), 3.88(s,3H,C_4,-OCH_3), 6.12(d,1H,C_7-H,J=10Hz), 6.82(s,1H,C_{10}-H), 7.00(d,2H,C_3,-H and C_5,-H,J=10Hz), 7.43(d,1H,C_6-H,J=10Hz), 7.52(d,2H,C_2,-H and C_6,-H,J=10Hz), 7.90(s,1H,C_5-H), 8.36(s,1H,C_2-H) (Found : C, 75.6 ; H, 5.4. $C_{21}H_{18}O_4$ requires 75.4 ; H, 5.4%).

(ii) Erythrinin A (10). The product was eluted with benzene-chloroform (70:30) in a silica gel column and crystallised from methanol to give pale yellow needles (30 mg), m.p. 161-62° (lit[1] 160-62°) ; IR : 3340, 1640, 1600 cm^{-1} (Found : C, 75.0 ; H, 4.8. $C_{20}H_{16}O_4$ requires C, 75.0 ; H, 5.0%).

Condensation of 6-acetyl-7-hydroxy-2,2-dimethylchromene with 4-methoxymethoxybenzaldehyde

Formation of 2'-hydroxy-4-methoxymethoxy-2'',2''-dimethyl-2H-pyrano(4',5':6'',5'')chalcone (7). To a solution of 6-acetyl-7-hydroxy-2,2-dimethylchromene[6](250 mg) in ethanol (20 ml), 4-methoxymethoxybenzaldehyde (230 mg) and aqueous KOH (30%, 10 ml) were added and the mixture stirred at room temperature for 36 h. Work-up of the reaction mixture gave a solid which crystallised from ethanol as red plates (150 mg), m.p. 112-13°, dark green ferric reaction; IR : 1630, 1600 cm^{-1}; PMR : δ 1.46 (s,6H,$(CH_3)_2C<$), 3.48(s,3H,C_4-OCH_3), 5.22(s, 2H,C_4-OCH_2-), 5.58(d,1H,C_3,-H,J=10Hz), 6.32(d,1H,C_4,-H,J=10Hz), 6.40(s,1H, C_3,-H), 7.07(d,2H,C_3-H and C_5-H,J=10Hz),7.30-7.52(m,4H,C_α and aromatic Hs), 7.88(d,1H,C_β-H,J=16Hz) (Found : C, 72.5 ; H, 6.1. $C_{22}H_{22}O_5$ requires C, 72.1 ; H,6.0%).

Rearrangement of 7 with TTN and acid cyclisation of 8

Synthesis of erythrinin A (10). To a solution of 7 (80 mg) in methanol (10 ml), a solution of TTN (120 mg) in TMOF (2 ml) was added slowly and the mixture stirred for 45 min. The filtrate containing 8 was refluxed with HCl (10%, 3 ml) for 4 h and worked up. The product crystallised from methanol as pale yellow needles (25 mg) m.p. 161-62° (lit[1] 160-62°) and was identical with the dehydrogenated product from 6 (m.m.p. and superimposable IR spectra); PMR : δ 1.48(s,6H,$(CH_3)_2C<$), 5.66(d,1H,C_7-H,J=10Hz), 6.32(s,1H,C_{10}-H), 6.62(d, 1H,C_6-H,J=10Hz), 6.88(d,2H,C_3,-H and C_5,-H,J=8Hz), 7.42(d,2H,C_2,-H and C_6,-H, J=8Hz), 7.88(s,1H,C_5-H), 5.42 (s,1H,C_4,-OH, D_2O exchangeable) (Found : C, 74.8 ; H, 5.1. $C_{20}H_{16}O_4$ requires C, 75.0 ; H, 5.0%).

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