SYNTHESIS OF NATURAL ISOFLAVANONES AND HOMOISOFLAVANONES*

By

L. FARKAS, A. GOTTSEGEN, M. NÓGRÁDI

Research Group for Alkaloid Chemistry, Hungarian Academy of Sciences at the Technical University, Budapest

and

S. ANTUS

Chinoin Pharmaceutical Works, Budapest

The systematic investigation of natural isoflavonoids has a tradition in the Institute of Organic Chemistry and was closely associated with the name of the late Professor ZEMPLÉN. The first synthesis of a natural isoflavon-glycoside [1], the determination of the structure [2] of sophorabioside, the first isoflavone-diglycoside and later on its synthesis [3] have all been carried out at our Institute.

Since in the last decade not only a large number of new isoflavones but many variants of the basic sceleton, differing in their oxidation state have been discovered, we started to work on the synthesis of isoflavanones and homoisoflavanones. The first representatives of the isoflavanone group ferreirin (2) and homoferreirin have been isolated in 1952 [4], while the first members of the homoisoflavanone series became known by the isolation of eucomin (25) and (-)-eucomol (26) [5] as late as in 1967.

Isoflavanones

The natural occurrence of nine isoflavanones, ferreirin (2) [4], homoferreirin [4], dalbergioidin (1) [6], ougenin (3) [6], sophorol (4) [7], nepseudin [8], neotenon [8], violanone [9] and 6,7-dimethoxy-3',4'-methylenedioxyisoflavanone [10] has been recorded. The existence of padmakastein as a 4',5-dihydroxy-7-methoxyisoflavanone [11] has been revised by our group [12] by carrying out its synthesis.

From the above mentioned isoflavanones we accomplished the first synthesis of ferreirin (2) [13], dalbergioidin (1) [13], and sophorol (4) [14] and a new synthesis of ougenin (3) [13, 15].

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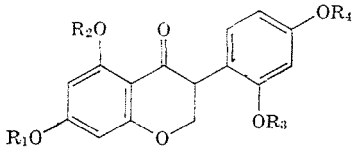
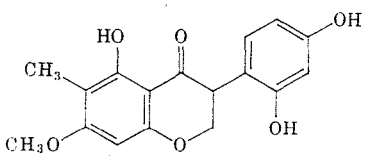
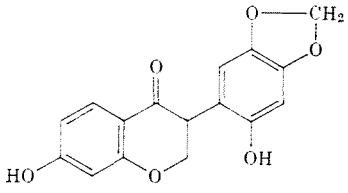


1: Dalbergioidin $R_1=R_2=R_3=R_4=H$
2: Ferreirin $R_1=R_2=R_3=H$, $R_4=CH_3$



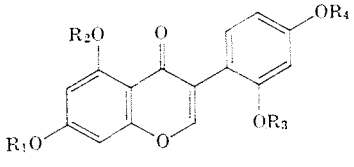
3: Ougenin



4: Sophorol

Syntheses of isoflavanones can be divided into two stages. First, an appropriately substituted isoflavone has to be synthesized which is then hydrogenated under carefully controlled conditions to yield the corresponding racemic isoflavanone.

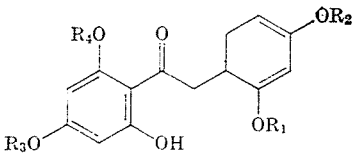
In our case the synthesis of the appropriately substituted isoflavones meant always the synthesis of the totally acetylated products, because it was the hydrogenation of the acetates over palladium-charcoal, in suitable solvents which could be stopped at the isoflavanone oxidation state.

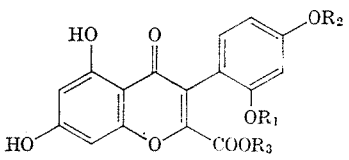


5: $R_1=R_2=R_3=R_4=Ac$
6: $R_1=R_2=R_3=Ac$; $R_4=CH_3$
7: $R_1=R_2=R_3=R_4=CH_3$
8: $R_1=R_2=R_3=R_4=H$
9: $R_1=CH_3$, $R_2=R_3=R_4=H$
13: $R_1=R_2=H$, $R_3=R_4=CH_3$

In order to synthesise *dalbergioidin* (1) the 2',4',5,7-tetramethoxyisoflavone (7) seemed to be a promising starting material, since its demethylation with aluminium chloride to the 2',4',5,7-tetrahydroxyisoflavone (8) has been described by WHALLEY [16]. But according to our investigations in this

reaction only partial demethylation took place and the resulting 7-methoxy derivative (9) could not be further dealkylated without the decomposition of the isoflavone ring system. Therefore the required tetrahydroxyisoflavone (8) had been prepared from 2,4,6-trihydroxyphenyl 2,4-dimethoxybenzyl ketone (10) and methoxalyl chloride [17].





10: $R_1=R_2=CH_3$, $R_3=R_4=H$
14: $R_1=PhCO$, $R_2=CH_3$, $R_3=R_4=H$
20: $R_1=H$, $R_2=R_4=CH_3$, $R_3=PhCH_2$

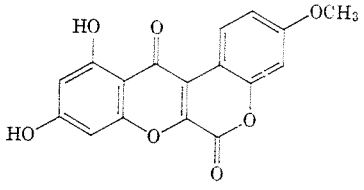
11: $R_1=R_2=R_3=CH_3$
12: $R_1=R_2=CH_3$, $R_3=H$
15: $R_2=R_3=CH_3$, $R_1=PhCO$
16: $R_1=R_3=H$, $R_2=CH_3$

The corresponding 2-carbomethoxyisoflavone (11) gave after mild alkaline hydrolysis the isoflavone-2-carboxylic acid (12), from which after thermal decarboxylation in the presence of copper-powder the isoflavone (13) was available. 13 obtained by this route had an OH-group at C-7, so its demethylation with hydroiodic acid gave in high yields 8. Acetylation of 8 gave 2',4',5,7-tetraacetoxyisoflavone (5) which on subsequent hydrogenation afforded crystalline racemic tetraacetoxyisoflavanone. Deacetylation of the latter led to (±)-2',4',5,7-tetrahydroxyisoflavanone, identical in every respect with those reported for natural dalbergioidin.

Our starting material for the synthesis of *ferreirin* (2) was again a deoxybenzoin (14) prepared from phloroglucinol and (2-benzoyloxy-4-methoxy phenyl) acetonitrile (obtained in five steps from 2-hydroxy-4-methoxy benzaldehyde via azlactone synthesis) under the conditions of the Hoesch synthesis. Treatment of this ketone with methoxalyl chloride resulted in the corresponding 2-carbomethoxy isoflavone (15). At this point our scheme would have required saponification, protection of the 2'-hydroxy group and decarboxylation. However this was prevented by ready lactonisation of the expected isoflavone 2-carboxylic acid (16) to the stable 9,11-dihydro-3-methoxy [1] benzopyrano [3, 4-b] [1] benzopyran-6,12-dione (17).

Because of this lactonisation the only possible route for carrying out the synthesis seemed to be the protection of the free hydroxyls in 15, and degradation of the 2-carbomethoxyisoflavone to a deoxybenzoin in which the phloroglucinol ring is sufficiently deactivated by the ether functions to permit ring closure with ethyl formate — sodium powder to afford a suitably substituted hydroxyisoflavone. Accordingly 15 was benzylated to yield

18, methylated to give 19 and degraded with methanolic alkali to 20, which was formylated to 21. On acidification the formyl-compound (21) cyclised via route A to 22.



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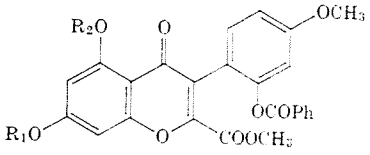
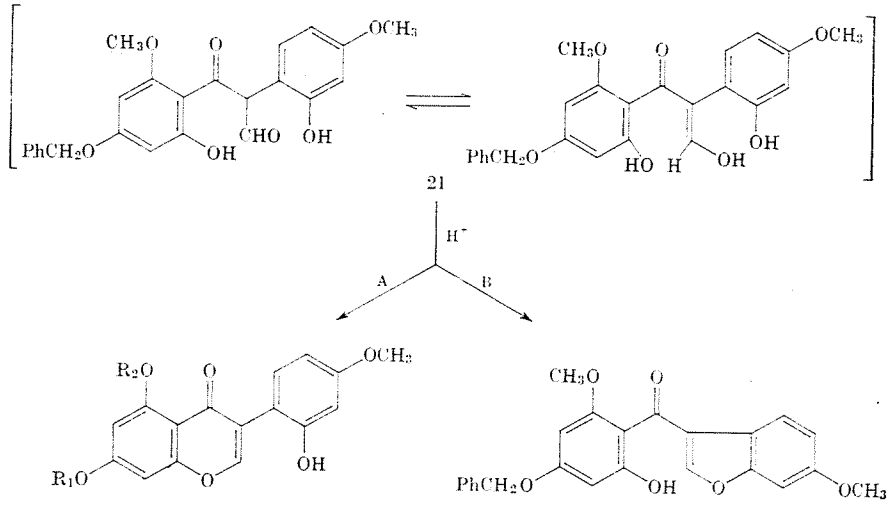


18: R_1=$PhCH_2$, R_2=H
19: R_1=$PhCH_2$, R_2=CH_3

22 was partially demethylated with aluminium chloride at C-5 to 23, which gave after debenzylation 24. Acetylation of 24 yielded 2',5,7-triacetoxy-4'-methoxyisoflavone (6). This was suitable for hydrogenation, affording the crystalline isoflavanone acetate, from which under mild acidic conditions



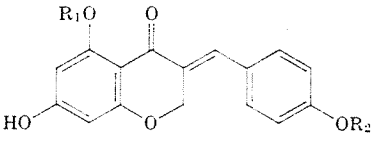
22: R_1=$PhCH_2$, R_2=CH_3
23: R_1=$PhCH_2$, R_2=H
24: R_1=R_2=H

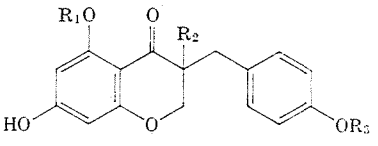
±)-2'5,7-trihydroxy-4-methoxyisoflavanone (2) identical in every respect with natural ferreirin was obtained.

Homoisoflavanones

In 1967 BÖHLER and TAMM [5] isolated eucomin (25) and (−)-eucomol (26), the first representatives of homoisoflavanones, a new class of naturally occurring oxygen heterocyclics. Homoisoflavanones are benzylidene- and benzyl chromanones. In 1970 TAMM, SIDWELL and FINCKH [18, 19] enriched this new group by the isolation of eight new compounds.

The synthesis and the structure determination of all the ten compounds, such as eucomin (25), eucomol (26), punctatin (29), (±)-3,9-dihydropunctatin (31), 4'-0-methylpunctatin (30), (±)-3,9-dihydro-4'-0-methylpunctatin (32), eucomnalin (33), (±)-3,9-dihydroeucomnalin (34), 4'-demethyleucomin (27) and (±)-4'-demethyl-5-0-methyl-3,9-dihydroeucomin (28) were carried out in our laboratory [20, 21].



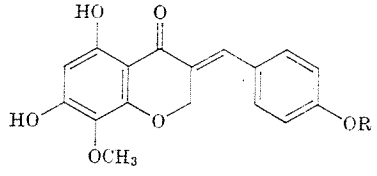


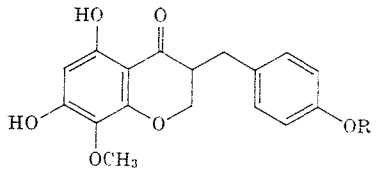
25: Eucomin: $R_1=H$, $R_2=CH_3$

26: Eucomol: $R_1=H$, $R_2=OH$ $R_3=CH_3$

27: 4'-Demethyleucomin: $R_1=R_2=H$

28: 4'-Demethyl-5-0-methyldihydro-eucomin: $R_1=CH_3$, $R_2=R_3=H$



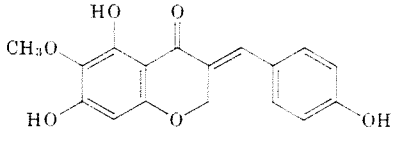


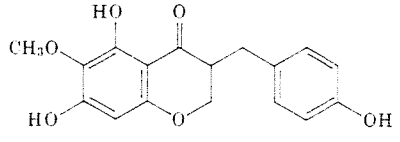
29: Punctatin: R=H

30: 4'-0-Methylpunctatin: $R=CH_3$

31: Dihydropunctatin: R=H

32: 4'-0-Methyl-dihydropunctatin: $R=CH_3$



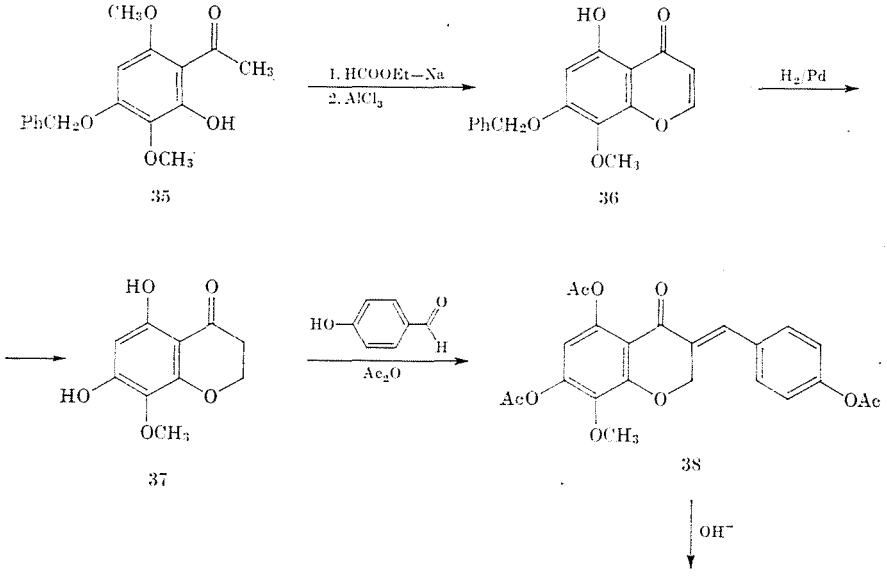


33: Eucomnalin

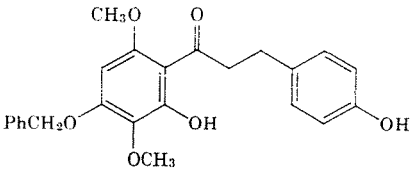
34: Dihydroeucomnalin

Although condensation methods for preparing benzylidene chromanones were well known from literature using either acid [22, 23] or alkali [24] as catalyst, these methods failed with our chromanones incorporating a phloroglucinol unit. The problem has been solved by the application of a method which had been worked out in our laboratory [25] for the synthesis of aurones. Similarly to coumaranones chroman-4-ones can be readily condensed with aromatic aldehydes in boiling acetic anhydride.

The general scheme exemplified by the synthesis of punctatin consisted of the ring closure of an appropriate 2-hydroxyacetophenone to chromone, of its conversion to the chromanone (35 → 36 → 37) followed by condensation with an aromatic aldehyde to yield the acetate of a 3-benzylidene-chroman-4-one (38). Saponification completed the synthesis of the natural compound (29).



Hydrogenation of 29 led to racemic dihydropunctatin (31) which is one of the representatives of natural benzylchromanones. Since of the ten new compounds four were benzylchromanones, it seemed to be important to work out a more convenient method for their syntheses [21]. We have found that similarly to deoxybenzoins the α-methylene group of the easily accessible dihydrochalcones (39) is sufficiently active to allow cyclisation with ethyl formate and sodium, giving another variant this group which can be denoted as homoisoflavones (40).



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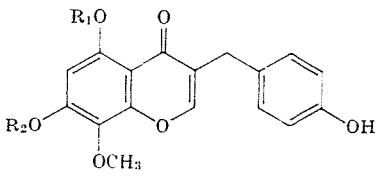
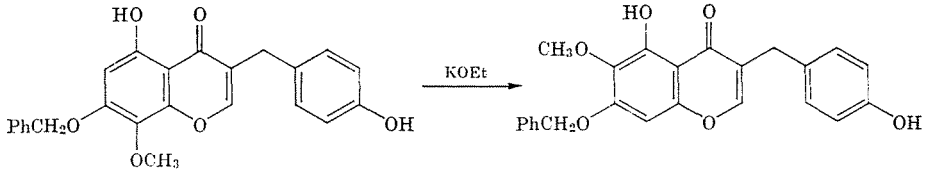


40: $R_1=CH_3$, $R_2=PhCH_2$
41: $R_1=R_2=H$

The homoisoflavones are closely related to isoflavones not only by name, but by their character as well. So similarly to the catalytic hydrogenation of isoflavones [12, 13, 14] homoisoflavones can readily be hydrogenated to the corresponding benzylchromanones (41 → 31). Furthermore the potassium ethoxide catalysed ring isomerisation of isoflavones [26] could be observed with this type as well (42 → 43).



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Summary

The first synthesis of two natural isoflavanones and the general scheme for the syntheses of all members of the recently discovered class of homoisoflavanones are reported.

References

1. Zemplén, G., Farkas, L.: Ber. der dtsch. chem. Ges. **76,** 1110 (1943).
2. Zemplén, G., Bognár, R.: Ber. der dtsch. chem. Ges. **75,** 482 (1942).
3. Farkas, L., Nógrádi, M., Wagner, H., Hörhammer, L.: Chem. Ber. **101,** 2758 (1968).
4. King, F. E., Grundon, M. F., Neill, K. G.: J. Chem. Soc. 4580, 1952.
5. Böhler, P., Tamm, Ch.: Tetrahedron Letters 3479 (1967).
6. Balakrishna, S., Ramanathan, J. D., Seshadri, T. R., Venkataramani, B.: Proc. Roy. Soc., 1962. A. **268,** 1.
7. Suginome, H.: J. Org. Chem., **24,** 1655 (1959).
8. Crombie, L., Whitind, D. A.: J. Chem. Soc. 1959, 1963.
9. Kurosawa, K., Ollis, W. D., Redman, B. T., Sutherland, I. O.: Chem. Comm. 1263 (1968).
10. Campbell, R. V. M., Harfer, S. H., Kemp, A. D.: J. Chem. Soc. (C) 1787, 1969.
11. Narasimhachari, N., Seshadri, T. R.: Proc. Indian Acad. Sci. **35A,** 202 (1952). Ramanujan, S., Seshadri, T. R.: ibid. **48,** 175 (1958).

12. FARKAS, L., NÓGRÁDI, M., ANTUS, S., GOTTSEGEN, Á.: Tetrahedron **25,** 1013 (1969).
13. FARKAS, L., GOTTSEGEN, Á., NÓGRÁDI, M., ANTUS, S.: J. Chem. Soc. (C) 1994, 1971.
14. FARKAS, L., NÓGRÁDI, M., GOTTSEGEN, A., ANTUS, S.: Chem. Comm. 825, 1972.
15. JAIN, A. C., LAL, P., SESHADRI, T. R.: Indian J. Chem. **7,** 61 (1969).
16. WHALLEY, W. B.: J. Chem. Soc. 1837, 1957.
17. BAKER, W., CHADDERTON, J., HARBORNE, J. B., OLLIS, W. D.: J. Chem. Soc. 1852, 1953.
18. SIDWELL, W. T. L., TAMM, CH.: Tetrahedron Letters 475 (1970).
19. FINCKH, R. E., TAMM, CH: Experientia **26,** 472 (1970).
20. FARKAS, L., GOTTSEGEN, Á., NÓGRÁDI, M.: Tetrahedron **26,** 2787 (1970).
21. FARKAS, L., GOTTSEGEN, Á., NÓGRÁDI, M., STRELISKY, J.: Tetrahedron **27,** 5049 (1971).
22. DANN, O., HOFFMANN, H.: Chem. Ber. **95,** 1448 (1962).
23. DANN, O., HOFFMANN, H.: Chem. Ber. **98,** 1498 (1965).
24. PFEIFFER, P., BREITH, E., HOYER, H.: J. prakt. Chem. **237,** 31 (1931).
25. FARKAS, L., PALLOS, L., HIDASI, G.: Chem. Ber. **94,** 2221 (1961).
FARKAS, L., PALLOS, L., NÓGRÁDI, M.: ibid., **97,** 1044 (1964); **98,** 2103 (1965).
26. FARKAS, L., VÁRADY, J.: Chem. Ber. **93,** 1269 (1960).

Dr. Loránd FARKAS
Dr. Ágnes GOTTSEGEN
Dr. Mihály NÓGRÁDI
Dr. Sándor ANTUS

1502 Budapest, P. O. B. 91. Hungary