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SYNTHESIS OF THE COUMARIN, GLABRALACTONE

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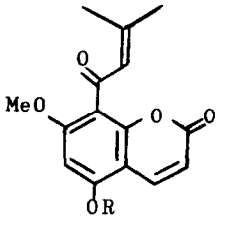
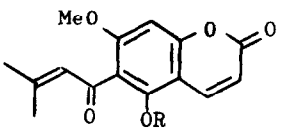
Whereas the natural coumarin, glabralactone,[1] has been assigned[2] structure (2) on the basis of rigorous degradative evidence, allocation[3] of the senecioyl side chain to C-6 in angelicone (4) has been less convincingly demonstrated. Later however the structure of the retro-aldol product from angelicone was revised[4] from 6-acetyl to 8-acetyl-5,7-dimethoxycoumarin. The implication that the two coumarins were therefore identical was in agreement with both having the same m.p., 130°. Nevertheless, in the three most important reviews[5] of natural coumarins, angelicone (4) and glabralactone (2) are classified as discrete compounds.

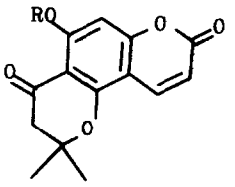
In order to clarify the situation, we decided to synthesise both structures from the known[6] phenol (5), the preparation of which can be simplified and improved by using malic acid in place of ethyl propiolate. We felt that it might be possible to convert the derived methyl ether (6) into 3 by a retro-Michael ring opening of the chromanone ring and that 1 was in principle derivable from 3 by a coumarin ring isomerisation process.[7] With this in mind, 6 was reacted with a 2-fold excess of NaOEt in EtOH at 40° for 5 hr. After acidification and separation by TLC, three isomeric coumarins were isolated; recovered 6 (33%), a mobile phenol, m.p. 152° (28%) and a very polar phenol, m.p. 190° (dec.) (39%). IR and NMR evidence indicates the presence of a senecioyl grouping in both phenols, the less polar of which also possesses a chelated hydroxyl (τ - 4.77) and must be represented by 3. In confirmation, 3 was reconverted to 6 in acidified EtOH, slowly at 20° but rapidly at 60°. Methylation of 3 (MeI, K_2CO_3, acetone) quantitatively afforded "angelicone" (4), m.p. 120°. Not unexpectedly, the UV and IR spectra found for 4 are not identical with those published[3] for natural



1 : R=H
2 : R=Me



3 : R=H
4 : R=Me



5 : R=H
6 : R=Me

angelicone. The very insoluble polar phenol from UV evidence also possesses a 5-OH and apart from the absence of chelation shows similar spectral behaviour to 3. That this was the ring isomerised phenol (1) was shown by its stability to cold acid and by its quantitative conversion to glabralactone (2), m.p. 129-130°, on methylation. Significantly the UV and IR spectra published[3] for angelicone were identical with those found for 2.

So far it has not been possible to obtain authentic samples of either natural angelicone or glabralactone for direct comparison.

References

1. T. Kariyone and K. Hata, J. Pharm. Soc. Japan, 76, 649 (1956)
2. K. Hata, J. Pharm. Soc. Japan, 76, 666 (1956)
3. M. Fujita and T. Furuya, J. Pharm. Soc. Japan, 76, 538 (1956)
4. T. Furuya and C.H. Ch'en, Yakugaku Zasshi, 81, 800 (1961)
5a. F.M. Dean, "Naturally Occurring Oxygen Ring Compounds", Butterworths, London, 1963
5b. T.O. Soine, J. Pharm. Sci., 53, 3 (1964)
5c. B.E. Nielsen, Dansk Tidsskr. Farm., 44, 111 (1970)
6. A.K. Ganguly, B.S. Joshi, V.N. Kamat and A.H. Manmade, Tetrahedron, 23, 4777 (1967)
7. C. Djerassi, E.J. Eisenbraun, R.A. Finnegan and B. Gilbert, J. Org. Chem., 25, 2164 (1960)