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OXIDATION OF FLAVAN DERIVATIVES

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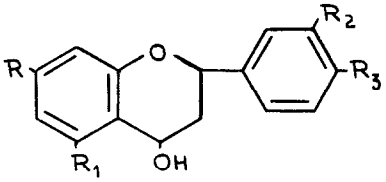
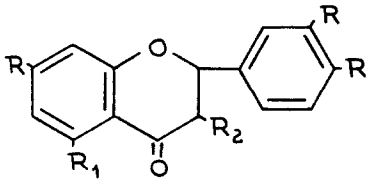
In the study of naturally occurring flavan derivatives with hydroxyl groups in the oxygen ring, oxidation is a useful reaction for conversion into other products. Some results obtained with different types of compounds and different reagents are summarised here. There is special interest in the behaviour of flavan-3,4-diols which are important components of proanthocyanidins.

Dimethyl sulphoxide is known to function as an oxidising agent for alcohols[1] and the use of dimethyl sulphoxide-acetic anhydride has therefore been examined. Flavan-4-ols (α and β), unsubstituted in the 5-position, are conveniently oxidised to flavanones. For example, simple flavan-4-ol (α and β) (I) m.p. 119° and 148° respectively and 7,3',4'-trimethoxy flavan-4β-ol (II) m.p. 136-7° have been fully oxidised to the corresponding flavanones (III) m.p. 76° and (IV) m.p. 120-1° respectively. But 5,7,4'-trimethoxy flavan-4-ol (V) m.p. 158° is recovered unchanged after 24 hr indicating that the 5-methoxyl group sterically hinders the oxidation; there is only a small degree of oxidation forming the flavanone even after 72 hr. However, the hydroxyl group in the 3-position is not affected by this steric hindrance and undergoes oxidation. l-Epi-catechin tetramethyl ether (VI) m.p. 153-4°, has been used as a typical example and gives corresponding 3-ketoflavan (VII) in low yield in 24 hr and about 30% in 72 hr. This has been characterised by the study of its I.R. spectrum (1715 cm^{-1} for CO) and the formation of a 2,4-dinitrophenylhydrazone, m.p. 138-40° (decom.). In the study of the mechanism of formation of anthocyanidins from flavan-3,4-diols, Robertson[2] recapitulated earlier

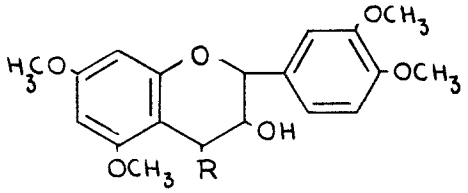
claims[3-5] of obtaining 3-ketoflavans and reported that they were based on uncertain evidence . His own efforts to prepare these compounds were unsuccessful. The present experiments provide evidence for the formation of 3-keto flavans.



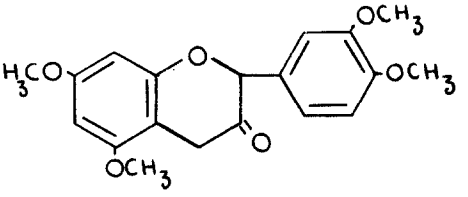
I R, R_1,R_2,R_3 = H
II R, R_2,R_3 = OCH_3; R_1=H
V R, R_1,R_3 = OCH_3; R_2=H



III R, R_1,R_2 = H
IV R = OCH_3; R_1,R_2 = H
X R,R_1 = OCH_3; R_2= OH



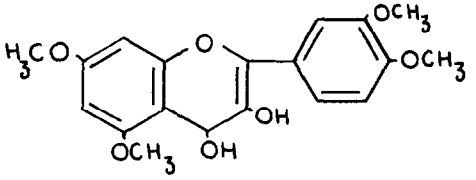
VI R = H
VIII R = OH



VII

As a more complex example, leucocyanidin tetra methyl ether (VIII) has been used for the oxidation. It was prepared from taxifolin tetramethyl ether by sodium borohydride reduction and purified by crystallisation from benzene.[6] In this case also the 3-hydroxyl group undergoes oxidation followed by enolisation to yield the ψ-base of cyanidin tetra methyl ether (IX) along with traces of quercetin tetra methyl ether. The ψ -base has been isolated in the form of the acetate. In order to confirm its identity this substance has been prepared from tetra-O-methylcyanidin chloride by treatment with acetic anhydride and pyridine, a method used earlier by Freudenberg[7] in other cases. Both the samples had the same behaviour on

T.L.C. (light petroleum: benzene: ethyl acetate, 20:2:3). The very small amount of quercetin tetramethyl ether obtained along with the ψ-base should be due to the further oxidation of the 4-hydroxyl to a small extent as it also happened in the case of 5,7,4'-trimethoxy flavan 4-ol.



IX

As a different type taxifolin tetramethyl ether (X) has also been oxidised. It gives rise to quercetin tetramethyl ether, m.p. 197-8°, in good yields along with a small amount of its 3-acetate, m.p. 160-3°. This conversion indicates that the oxidation is not hindered by the presence of the keto group.

In all these cases 1m mole of the starting material was treated with 3 ml of dimethyl sulphoxide and 2 ml of acetic anhydride and kept at room temperature for 24 hr[8]; the mixture was then poured into water and extracted with ether or ethyl acetate.

Selenium dioxide-pyridine behaved similar to DMSO. A mixture of leucocyanidin tetramethyl ether (100 mg) in pyridine and excess of the pyr. complex (500 mg) was refluxed for 10 hr. The selenium that separated was filtered off and the solvent evaporated under reduced pressure. The residue was treated with cold dil. HCl when a flavylium salt (65 mg) separated and it was identified as tetra-O-methyl cyanidin chloride; for paper chromatography Forestal solvent, HCl : HOAc : Water : 3:30:10 is convenient.

Chromium trioxide-pyridine differed in its action and seemed to affect only the 4-hydroxyl group. An ice-cold slurry of pyridine-CrO_3 complex (200 mg) was stirred for 1 hr with pyridine solution of leucocyanidin tetramethyl ether (200 mg). The mixture was left at room temperature for

16 hr and then treated with ice cold HCl. On ether extraction of the acidulated solution, a pale yellow solid (60 mg) separated and was identified as taxifolin tetramethyl ether. The product was contaminated with a small amount of quercetin tetramethyl ether resulting from further oxidation.

Fremy's Salt resembled CrO_3 though the yield was very small. Leucocyanidin tetramethyl ether (200 mg) in methanol (50 ml) was treated with an aqueous solution of Fremy's salt (2.5 g in 50 ml water) at room temperature in the presence of a small amount of NaOAc (0.1N; 40 ml). The mixture was stirred till the colour of the reagent was discharged and then ether extracted. T.L.C. study of the extract showed that the conversion was small, most of the starting material being recovered. The yield of the oxidised product after purification by T.L.C. was small (10 mg).

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REFERENCES

1. W.W. Epstein and F.W. Sweat, Chem. Reviews, 67, 247, 1967.
2. A.V. Robertson, Can. J. Chem., 37, 1946, 1959.
3. P. Karrer and W. Fatzer, Helv. Chem. Acta, 25, 1129, 1942.
4. E. L. Fousenka, J. Chem. Soc., 1683, 1947.
5. P. Karrer and M. Seyhau, Helv. Chem. Acta, 33, 2209, 1950.
6. A. K. Ganguli and T.R. Seshadri, Tetrahedron, 6, 21, 1959.
7. K. Freudenberg, Karimullah, and G. Steinbrunn, Annalen, 518, 37, 1935.
8. J. D. Albright and L. Goldman, J. Am. Chem. Soc., 87, 4215, 1965.