ACTA CHEMICA SCANDINAVICA 7 (1953) 1323—1330

The Structure of Some Alleged 3-Hydroxyflavanones

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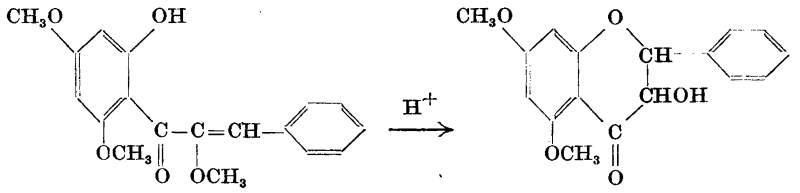
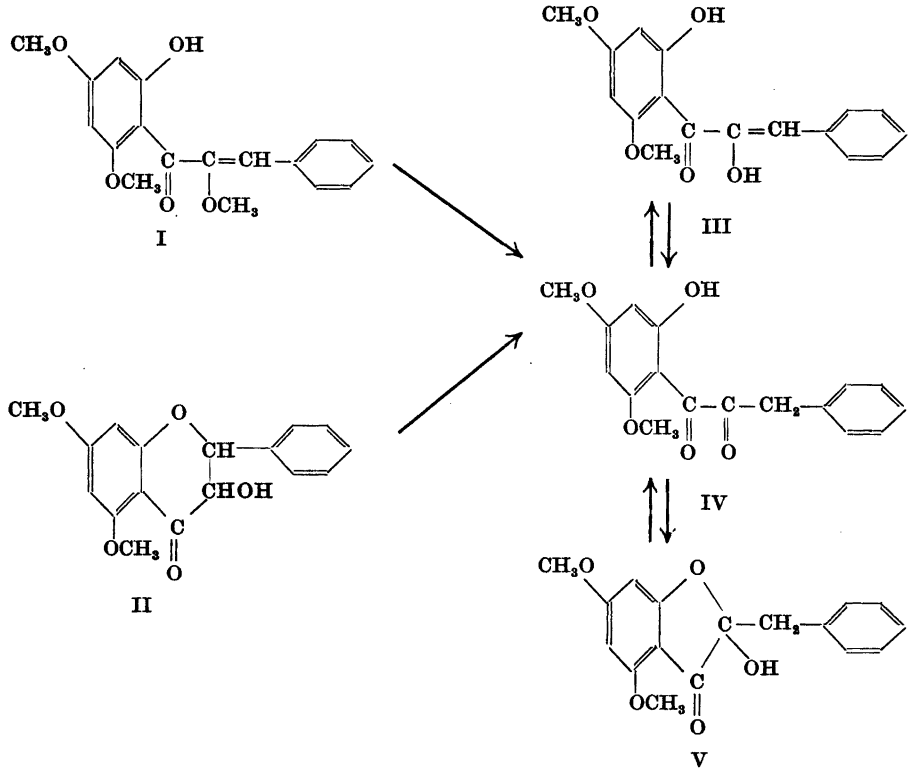
Some years ago Lindstedt [1] showed that the so-called apoalpinonemonomethylether of Kimura could not have the structure assigned to it [2]. Kimura obtained the compound by condensing 2-hydroxy-ω,4,6-trimethoxyacetophenone with benzaldehyde and treating the resulting chalcone (I) with acid; he assumed that hydrolysis of the enolether was followed by ringclosure to a flavanone, giving 3-hydroxy-5,7-dimethoxyflavanone (II)



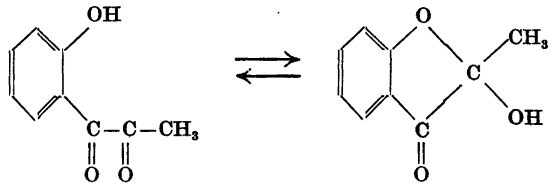
I II

Lindstedt [1], found that "apoalpinonemonomethylether" could also be obtained by treatment of pinobanksindimethylether (3-hydroxy-5,7-dimethoxyflavanone) with alkali, and subsequent acidification, but that it was soluble in alkali and did not give the colour reaction with magnesium and hydrochloric acid, typical of flavanones. It was thus clear that the compound was not a flavanone, but Lindstedt made no attempt to elucidate its true structure.

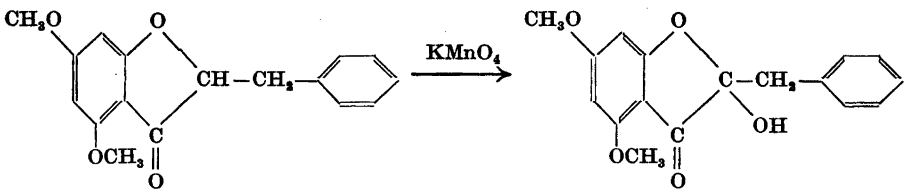
Bearing in mind that the compound is formed both by acid hydrolysis of 2′-hydroxy-ω,4′,6′-trimethoxychalcone (I), and by treatment of pinobanksindimethylether (II) with alkali, it is apparent that the most probable structure is represented by one of the three tautomeric formulae (III), (IV) or (V), the reactions being:



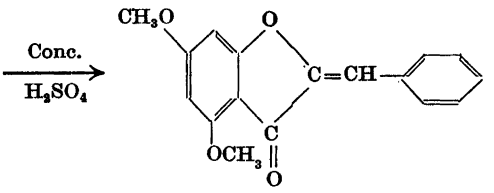
Of these formula (V) is the most probable, for the following reasons: (1) v. Auwers and Müller[3,4] have shown that attempts to prepare compounds of the type (VI) invariable lead to products whose properties were better represented by the tautomeric formula (VII).



(V) is a derivative of (VII). (2) "Apoalpinonemonomethylether" upon treatment with conc. sulphuric acid loses one molecule of water, giving 2-benzal-4,6-dimethoxycoumaranone (IX). (3) It can also be obtained by oxidation of 2-benzyl-4,6-dimethoxycoumaranone (VIII) with potassium permanganate.



VIII V

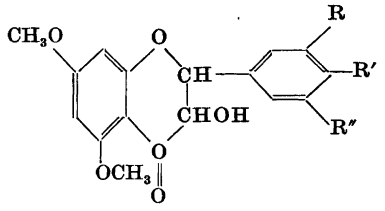


IX

This last mentioned reaction is closely analogous to the oxidation of a degradation product of griseofulvin [5].

Although there is always some uncertainty in deciding between tautomeric structures on the basis of chemical reactions, it is felt that structure (V) best explains the behaviour of the "apoalpinonemonomethylether", which is thus 2-benzyl-2-hydroxy-4,6-dimethoxycoumaranone.

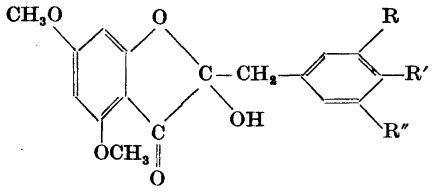
Kimura [6] has used the same method for the synthesis of some other alleged 3-hydroxyflavanones namely: 3-hydroxy-4′,5,7-trimethoxy-(X), 3-hydroxy-3′,4′,5,7-tetramethoxy-(XI), 3-hydroxy-3′,4′,5,5′,7-pentamethoxy-(XII) and 3-hydroxy-3′,4′-methylenedioxy-5,7-dimethoxyflavanone (XIII)



X; R = R″ = H; R′ = OCH_3
XI; R = H; R′ = R″ = OCH_3
XII; R = R′ = R″ = OCH_3
XIII; R = H; R′ + R″ = OCH_2O

Although it has not been proved experimentally, analogy makes it very reasonable to regard these compounds also as substituted 2-benzyl-2-hydroxy-

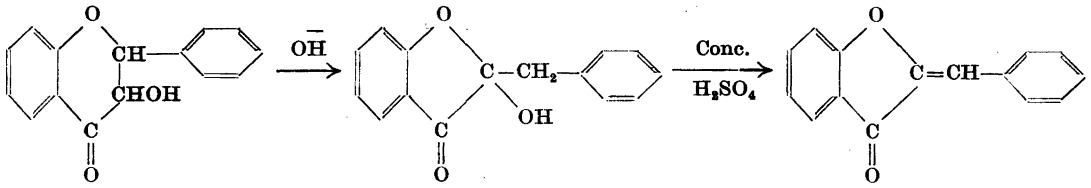
coumaranones, namely: 2-(4-methoxybenzyl)-(XIV), 2-(3,4-dimethoxybenzyl)-(XV) 2-(3,4,5,-trimethoxybenzyl)-(XVI) and 2-(3,4-methylenedioxybenzyl)-2-hydroxy-4,6-dimethoxycoumaranone (XVII) respectively.



XIV; R = R″ = H; R′ = OCH_3
XV; R = H; R′ = R″ = OCH_3
XVI; R = R′ = R″ = OCH_3
XVII; R = H; R′ + R″ = OCH_2O

Of these compounds (XVI) has been synthesised, apparently independently, by Kotake and Kubota [7], using the same method. But these authors obtained it also by treatment of ampelopsinpentamethylether (XII) with alkali, a reaction quite analogous to the formation of (V) from pinobanksindimethylether (II). Kotake and Kubota [7] regarded their product as a stereoisomer of ampelopsinpentamethylether and called it epiampelopsinpentamethylether. This view was supported by the ultraviolet absorption spectrum of "epiampelopsinpentamethylether", which was found to be almost identical with the spectrum of ampelopsinpentamethylether. However the similarity of the spectra is not at all incompatible with the structure (XVI) for "epiampelopsinpentamethylether", which has the same chromophore as the corresponding 3-hydroxyflavanone, and indeed can be taken as a further support for a structure of the type (V) in preference to (III) or (IV). A more detailed study of the ultraviolet absorption of the 2-benzyl-2-hydroxycoumaranones and the corresponding flavanones and chalcones is planned.

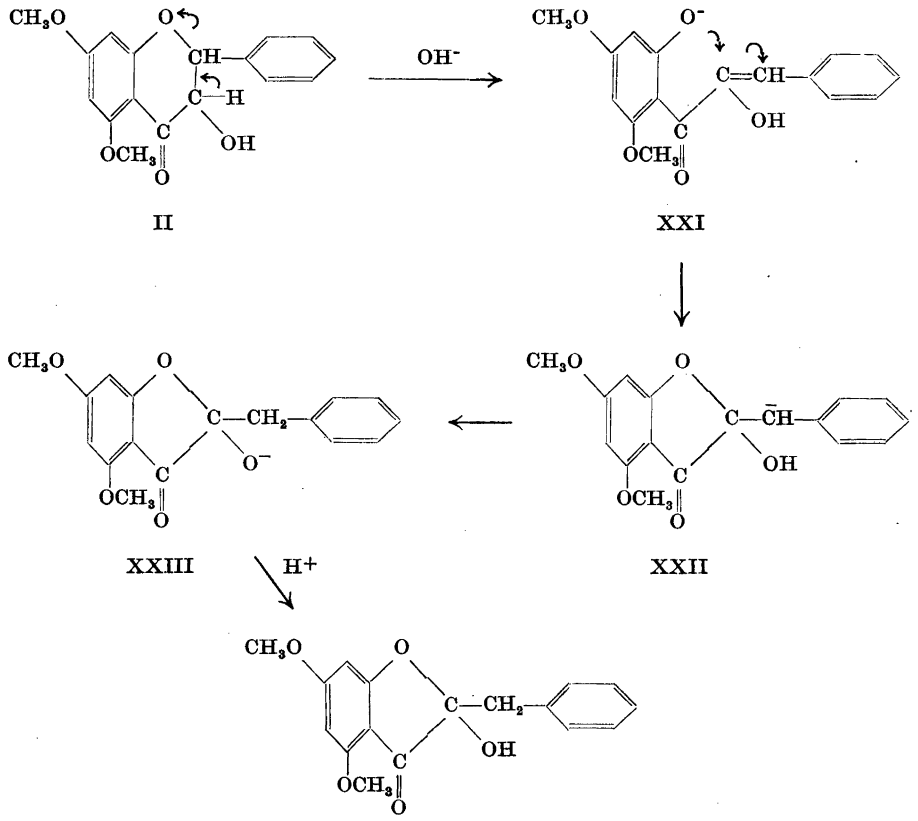
Geissman and Fukushima [8] have described a method of converting suitably substituted chalcones into benzalcoumaranones by means of hydrogen peroxide and alkali. It was demonstrated that there must be a methoxyl group in the 6′-position of the chalcone in order to give a benzalcoumaranone, which will thus have a methoxyl group in its 4-position. In order to find whether the formation of the coumaranone ring from 3-hydroxyflavanones is similarily dependent on the presence of a methoxyl group in the same position, — that is the 5-position in the flavanone —, 3-hydroxyflavanone (XVIII) was treated with alkali unde the same conditions as in the earlier cases. There was obtained, together with considerable amounts of 3-hydroxyflavone, an alkali soluble compound, isomeric with the starting material, which upon treatment with conc. sulphuric acid was converted into 2-benzalcoumaranone (XX). The compound must therefore be regarded as 2-benzyl-2-hydroxycoumaranone (XIX), and is apparently identical with the unidentified solid of m.p. 105—106°, obtained by Marathe, Chandorkar and Limaye [9] under similar conditions.



XVIII XIX XX

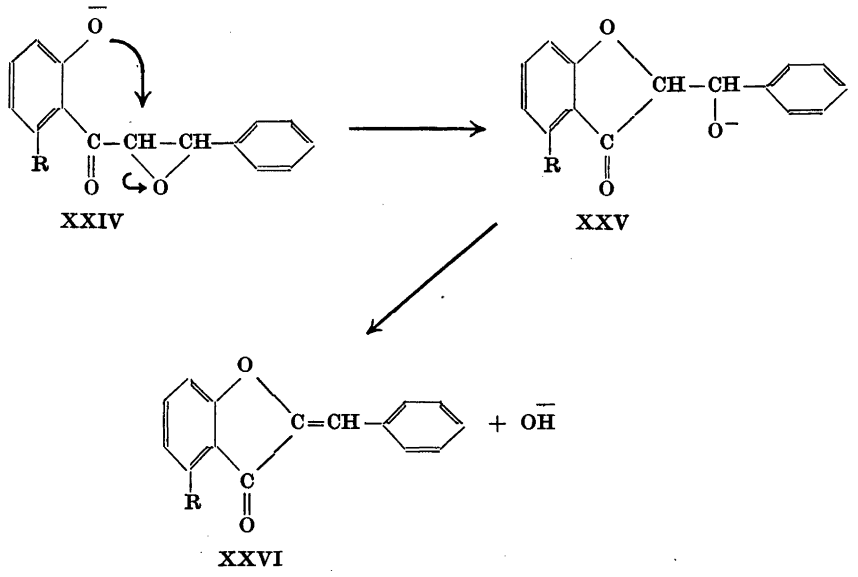
Thus the formation of the coumaranone ring in this case takes place even when there is no methoxyl group whatsoever in the molecule.

The following mechanism is proposed for the formation of a 2-benzyl-2-hydroxycoumaranone from the 3-hydroxyflavanone by treatment with alkali:



II XXI XXII XXIII V

The intermediates (XXI) and (XXII) are, however, those which Geissman and Fukushima [8] have proposed as intermediates in the formation of 2-benzalcoumaranones from chalcones. It is of course very improbable that the intermediates should be the same, as both reactions occur under almost identical conditions. It is therefore proposed that the formation of 2-benzalcoumaranone takes place in the following way:



In agreement with Geissman and Fukushima [8] the first step is considered to be the formation of the chalcone oxide ion (XXIV), the oxide ring of which is then opened by attack of the electron pair of the negatively charged oxygen atom — but opened in the opposite direction to that proposed by Geissman and Fukushima —, leading to (XXV). This is of course the intermediate which must also be assumed to be formed in the preparation of benzalcoumaranone from coumaranone and benzaldehyde under alkaline conditions. The discussion of Geissman and Fukushima regarding the influence of the group R on the course of the reaction holds equally well for this mechanism.

EXPERIMENTAL

2-Benzyl-4,6-dimethoxycoumaranone (VIII). 2-Benzal-4,6-dimethoxycoumaranone [8] (0.63 g) was hydrogenated in alcoholic solution over $Pt(O_2)$-catalyst. The uptake of hydrogen amounted to 56 ml (Calc. for 1 mole 53 ml). The catalyst was removed and the alcohol was evaporated *in vacuo* until crystallisation set in. The crystals (0.43 g) were collected. Addition of water to the mother liquor precipitated a further amount (0.15 g) of slightly less pure compound. The 2-benzyl-4,6-dimethoxycoumaranone after recrystallisation from dilute alcohol had m.p. 109.5 – 110.5° (Found: C 71.6; H 5.75. $C_{17}H_{16}O_4$ requires C 71.8; H 5.7 %).

2-Benzyl-2-hydroxy-4,6-dimethoxycoumaranone (V). 2-Benzyl-4,6-dimethoxycoumaranone (0.1 g) was dissolved in acetone (50 ml); a few drops of 2 *N* sodium carbonate and finely powdered potassium permanganate (0.3 g) were added. After standing for four days at room temperature the mixture was poured into water, acidified, and the manganese dioxide dissolved by introducing sulphur dioxide. The aqueous solution was thoroughly extracted with ether and the ether solution first washed with sodium hydrogen carbonate and then extracted with 2 *N* sodium hydroxide. The sodium hydroxide extract acquired a yellow colour. Acidification caused the 2-benzyl-2-hydroxy-4,6-dimethoxycoumaranone (0.03 g) to be precipitated in an almost pure condition. After crystallisation from dilute alcohol it had m.p. 170—170.5°. No depression was observed when mixed with "apoalpinonemonomethylether" prepared by Lindstedt [1] from pinobanksindimethylether (The author wishes to thank Prof. H. Erdtman for supplying this specimen). (Found: C 67.4; H 5.4. $C_{17}H_{16}O_5$ requires C 68.0; H 5.4 %.)

2-Benzal-4,6-dimethoxycoumaranone (IX) 2-Benzyl-2-hydroxy-4,6-dimethoxycoumaranone (0.02 g) was dissolved in conc. sulphuric acid (2 ml) giving an orange coloured solution. The solution was immediately poured into water (50 ml), and the slightly yellow precipitate was collected and crystallised from dilute alcohol. The m.p., 151.5—152.5° was undepressed, when the compound was mixed with an authentic specimen of 2-benzal-4,6-dimethoxycoumaranone prepared by the method of Geissman and Fukushima [8].

3-Hydroxyflavanone (XVIII) was prepared by the method of Murakami and Irie [10]. Crystallisation from alcohol gave a m.p. of 185—187° (Murakami and Irie [10] report m.p. 174—177°, Geissman and Fukushima [8] 177—180°, whereas Oyamada [11] for a sample prepared in another way reports 183—184°).

2-Benzyl-2-hydroxycoumaranone (XIX). 3-Hydroxyflavanone (1.0 g) was boiled for five minutes with a 5 % alcoholic potassium hydroxide solution (100 ml), in a stream of nitrogen. The solution was then rapidly cooled and poured into 2 *N* hydrochloric acid (200 ml). The precipitate was collected (0.3 g) and crystallised from alcohol to m.p. 165—167°. (A m.p. of 169—170° is reported for 3-hydroxyflavone [12]). The alcohol was removed from the mother liquor which was then extracted with ether. The ether solution was washed with sodium hydrogen carbonate solution and then extracted with 2 *N* sodium hydroxide. The yellow alkaline solution was acidified whereupon an oil, that partly solidified, was precipitated. The solid material was collected (0.1 g) and crystallised from ether — light petroleum to m.p. 102—103° (Found: C 74.85; H 5.05. $C_{15}H_{12}O_3$ requires C 75.0; H 5.0 %).

2-Benzalcoumaranone. 2-Benzyl-2-hydroxycoumaranone was converted into 2-benzalcoumaranone by the method described above for 2-benzyl-2-hydroxy-4,6-dimethoxycoumaranone. The m.p., 110—111°, after crystallisation from dilute alcohol, was undepressed when the compound was mixed with an authentic specimen of benzalcoumaranone.

SUMMARY

It has been shown that the alleged 3-hydroxyflavanones prepared by the method of Kimura are in fact substituted 2-benzyl-2-hydroxycoumaranones. These can also be obtained by rearrangement of the true 3-hydroxyflavanones. The mechanism of this rearrangement and that of the formation of 2-benzalcoumaranones from chalcones, discovered by Geissman and Fukushima, are discussed.

REFERENCES

1. Lindstedt, G. *Acta Chem. Scand.* **4** (1950) 772.
2. Kimura, Y. *J. Pharm. Soc. Japan.* **57** (1937) 160; *Chem. Abstracts* **33** (1939) 531.
3. v. Auwers, K. *Ber.* **47** (1914) 3292.
4. v. Auwers, K., and Müller, W. *Ber.* **50** (1917) 1149.
5. Grove, J. F., Ismay, D., MacMillan, J., Mulholland, T. P. C., and Rogers, M. A. T. *J. Chem. Soc.* **1952** 3958.

6. Kimura, Y. *J. Pharm. Soc. Japan.* **58** (1938) 415; *Chem. Abstracts* **32** (1938) 6649.
7. Kotake, M., and Kubota, T. *Ann.* **544** (1940) 253.
8. Geissman, T. A., and Fukushima, D. K. *J. Am. Chem. Soc.* **70** (1948) 1686.
9. Marathe, K. G., Chandorkar, K. R., and Limaye, S. D. *Rasayanam 2* (1952) N:o 2, 48. *Chem. Abstracts* **47** (1953) 6942.
10. Murakami, M., and Irie, T. *Proc. Imp. Acad. (Tokyo)* **11** (1935) 229. *Chem. Abstracts* **29** (1935) 6598.
11. Oyamada, T. *J. Chem. Soc. Japan* **64** (1943) 331; *Chem. Abstracts* **41** (1947) 3797.
12. v. Kostanecki, S., and Szabrański, W. *Ber.* **37** (1904) 2819.

Received October 15, 1953.