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SCOPE OF ISOFLAVONE SYNTHESIS USING 2'-BENZYLOXYCHALKONE EPOXIDES*

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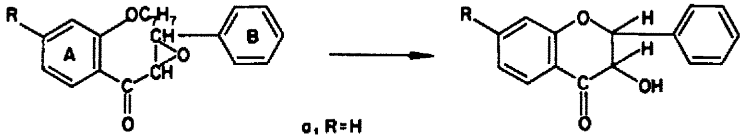
Abstract—Boron trifluoride-etherate reacts with 2'-benzyloxychalkone epoxides to give mainly dihydroflavonols if ring B is unsubstituted, but isoflavones are formed by rearrangement if methoxy groups are present in positions 4 or 3 and 4. These factors limit the applicability of isoflavone synthesis using chalkone epoxides.

IN AN earlier paper,[1] following a possible path of biogenesis, chalkone epoxides were used as intermediates for the synthesis of isoflavones. This reaction depends on: (i) boron trifluoride-etherate being used to bring about aroyl migration and (ii) protection of the 2'-hydroxy group by benzylation which has the advantage that mild conditions bring about debenzylation as well as cyclization.

In a later paper,[2] it was reported that in the presence of acidic reagents such as ethereal hydrogen chloride, acetic acid or halogen acids in acetic acid the reaction with 2'-benzyloxychalkone epoxides depends on the presence of substituents in the ring B as well as on the reaction conditions. As boron trifluoride-etherate is an acidic reagent (Lewis acid), its action on different epoxides was examined.

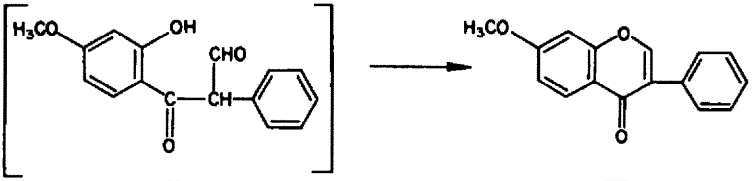
Simple 2'-benzyloxychalkone epoxide[2] (Ia) on treatment with boron trifluoride-etherate gives only 3-hydroxyflavanone (IIa) in good yield. Similarly, 2'-benzyloxy-4'-methoxychalkone epoxide[2] (Ib) gives the corresponding 7-methoxy-3-hydroxyflavanone (IIb) as the major product and in addition, small amounts of 2-hydroxy-4-methoxy-α-formyldesoxybenzoin (III) which as the alkali soluble portion of the reaction product gives 7-methoxyisoflavone (IV) on acidification. Chopin and Durual[3] reported similar results for these two chalkone epoxides (Ia and Ib) except that in the case of Ib, the presence of III was apparently overlooked.



I

a, R=H
b, R=OCH$_3$

II



III

IV

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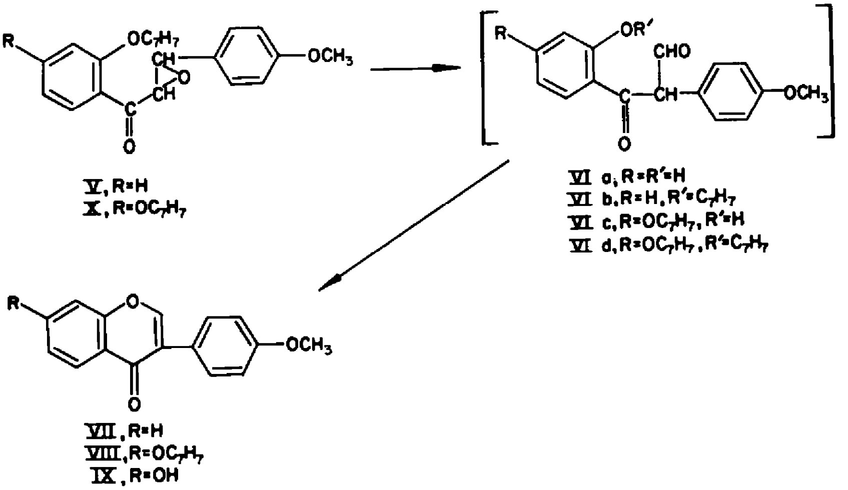
* For preliminary communication on this subject, see *Curr. Sci.* **33**, 240 (1964).

[1] S. K. Grover, A. C. Jain and T. R. Seshadri, *Ind. J. Chem.* **1**, 517 (1963).

[2] S. C. Bhrara, A. C. Jain and T. R. Seshadri, *Curr. Sci.* **33**, 48 (1964); *Tetrahedron* **20**, 1141 (1964).

[3] J. Chopin and P. Durual, *C.R. Acad. Sci., Paris* **257**, 700 (1963).

When the ring B of the chalkone epoxide is substituted, the isomerization reaction predominates. Thus 2′-benzyloxy-4-methoxychalkone epoxide (V) gives a mixture of two desoxybenzoins and 4′-methoxyisoflavone (VII). The desoxybenzoins after separation from ethereal solution of the reaction mixture and crystallization yield more isoflavone (VII) derived from the 2-hydroxy-4′-methoxy-α-formyl desoxybenzoin (VIa) present in the original mixture. The mother liquor from the crystallization with a positive ferric chloride reaction due to the presence of 2-benzyloxy-4′-methoxy-α-formyldesoxybenzoin (VIb), on heating with a mixture of hydrochloric and acetic acids yielded more isoflavone (VII), giving a total yield of about 80%, based on the original chalkone epoxide (V). This isoflavone has been prepared for the first time and its spectrometric data recorded.



V, R=H
X, R=OC_7H_7

VI a, R=R′=H
VI b, R=H, R′=C_7H_7
VI c, R=OC_7H_7, R′=H
VI d, R=OC_7H_7, R′=C_7H_7

VII, R=H
VIII, R=OC_7H_7
IX, R=OH

The reaction of 4-methoxy-2′,4′-dibenzyloxychalkone epoxide (X) with boron trifluoride-etherate similarly yields a mixture of α-formyldesoxybenzoins (VIc and VId) and isoflavone (VIII), and the total yield of isoflavone after conversion is the same as reported by Grover *et al.*[1] who first reported the reaction.

Similarly 2′-benzyloxy-3,4,4′-trimethoxychalkone epoxide (XIII) yields mostly the formyl derivative which undergoes change into 7,3′,4′-trimethoxyisoflavone (XIV) in good yield. This compound agrees in all respects with the natural product cabreuvin.[4] Although, synthesized earlier by other methods,[5] the present synthesis is far more convenient because of the simplicity of the starting materials.

2′-Benzyloxy-3,4,3′,4′-tetramethoxychalkone epoxide (XVI) proved difficult to crystallize and was directly used for the reaction with boron trifluoride-etherate. The identity of this epoxide was established by conversion to the crystalline chlorohydrin. Reaction with boron trifluoride-etherate yielded 7,8,3′,4′-tetramethoxyisoflavone (XVII) identical with the sample prepared by Kukla and Seshadri.[6]

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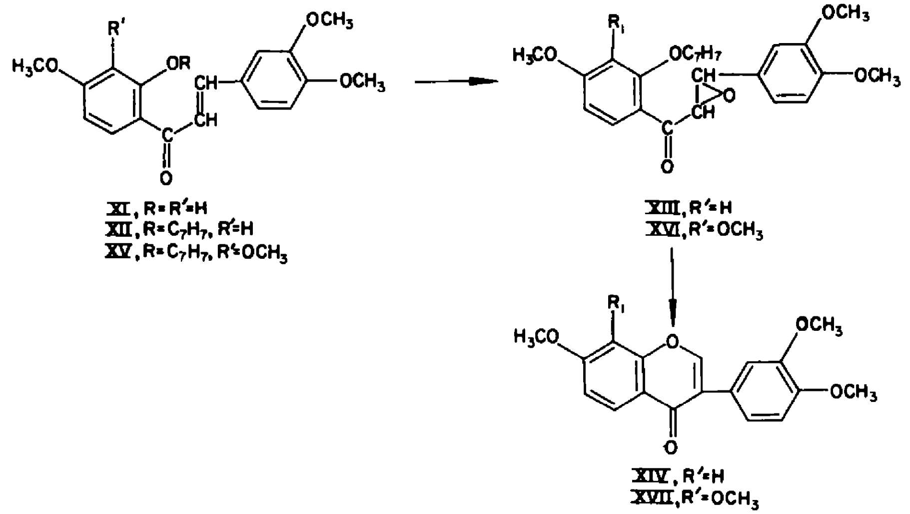
[4] O. R. Gottlich and T. Magalhaes, *Ann. Assoc. Brasileira Quinn.* **18**, 89 (1959).

[5] M. L. Dhar, N. N. Chari and T. R. Seshadri, *J. Sci. Industr. Res. India* **14B**, 73 (1955); L. Farkas, A. Major, L. Pallos and J. Varady, *Chem. Ber.* **91**, 2858 (1958); K. Fukui, M. Nakayama and M. Hatanaka, *Nippon Kagaku Zasshi* **84**, 189 (1963); *Chem. Abstr.* **59**, 13926 h (1963).

[6] A. S. Kukla and T. R. Seshadri, *Tetrahedron* **18**, 1443 (1963).



Substitution in the 2 or 2 and 4 positions as in 2'-benzyloxy-2,4'-dimethoxy- and 2'-benzyloxy-2,4,4'-trimethoxychalkone epoxides failed to yield crystallizable products.

As the reaction of chalkone epoxides with boron trifluoride-etherate varies in accordance with the substituents of ring B, it is applicable only to such isoflavones as have methoxy or methylenedioxy substituents in either 4' or 3' and 4' positions. In these cases, however, this method is advantageous because of the accessibility of the starting materials and the good yields obtained. Further, boron trifluoride-etherate is the most satisfactory reagent, although other reagents also give the same products.[2]

EXPERIMENTAL

M.p.s are uncorrected. Unless otherwise stated, UV spectra were measured in 95% EtOH and IR spectra on a Perkin-Elmer infracord spectrophotometer model 137 and KBr disc. The figures written in brackets after the maxima values in UV spectra represent log ε values. The light petroleum used had b.p. 40–60°.

Reaction of 2'-benzyloxychalkone epoxide (Ia)

Formation of 3-hydroxyflavanone, (IIa). Boron trifluoride-etherate (0·5 ml) was added to a solution of the epoxide[3] (Ia, 0·5 g) in dry benzene (10 ml) and the mixture shaken for 20 min at room temp. Ether (50 ml) was added and the solution washed well with water (2 × 50 ml). The organic layer was evaporated *in vacuo* and the solid residue crystallized from EtOH yielding IIa as colourless needles (0·3 g), m.p. and mixed m.p. with an authentic sample[3] 187–188°.

Reaction of 2'-benzyloxy-4'-methoxychalkone epoxide (Ib)

Formation of 3-hydroxy-7-methoxyflavanone (IIb) *and 7-methoxyisoflavone* (IV). The chalkone epoxide[3] (Ib, 1 g) in benzene (20 ml) was treated with BF_3-etherate (1 ml) and worked up as described in the previous experiment. The ether–benzene solution obtained after washing with water was extracted with 5% NaOHaq leaving the ether–benzene solution (A). The alkali solution was acidified, cooled and extracted with ether. The ether extract was evaporated and the residue crystallized from MeOH yielding IV (ca. 10 mg) as colourless plates, m.p. and mixed m.p. with an authentic sample 154–155°.

The ether–benzene solution (A) on evaporation yielded IIb[3] (0·2 g) which crystallized from ethyl acetate–light petroleum as colourless needles, m.p. and mixed m.p. 148–149°.

Reaction of 2′-benzyloxy-4-methoxychalkone epoxide (V)

Formation of 4′-methoxyisoflavone, (VII). The epoxide[2] (V, 1 g) in benzene (20 ml) was treated with BF_3-etherate (1 ml) and the product worked up as described above. The benzene–ether layer was extracted with 5% NaOHaq yielding an alkaline solution (A). The organic layer was evaporated *in vacuo* and the residue (VII) crystallized from ethyl acetate–light petroleum as colourless rectangular plates (0·2 g), m.p. 138–140°; λ_{max} 252 mμ (4·2), 307 mμ (3·6); ν_{max} 1640 cm^{-1} (C=O). (Found: C, 76·1; H, 4·7; $C_{16}H_{12}O_3$ requires: C, 76·2; H, 4·8%).

The alkaline solution (A) was acidified and extracted with ether. The ether residue crystallized from ethyl acetate–light petroleum as colourless rectangular plates (0·2 g), m.p. and mixed m.p. with 4′-methoxyisoflavone 138–140°. The mother liquor gave a positive ferric chloride reaction and was evaporated to dryness. The residue was heated with a mixture of acetic acid (10 ml) and HClaq (15 ml) and the product neutralized with 5% NaOHaq, yielding a solid which on crystallization was found to be 4′-methoxyisoflavone (0·1 g); total yield of isoflavone (V) 0·5 g.

Reaction of 4-methoxy-2′,4′-dibenzyloxychalkone epoxide (X)

Formation of 7-O-benzylformononetin (VIII) *and formononetin* (IX). The epoxide[1] (X, 1 g) in benzene (20 ml) was reacted with BF_3-etherate (1 ml) and the reaction product worked up as above. The alkali insoluble fraction after crystallization from ethyl acetate–EtOH afforded 7-O-benzylformononetin (0·1 g) as colourless plates, m.p. and mixed m.p. with an authentic sample[2] 180–182°, whereas the alkali soluble fraction on working up gave 7-O-benzylformononetin (0·2 g) and formononetin (0·1 g) as colourless small plates, m.p. and mixed m.p. with an authentic sample[2] 254–255°.

Preparation and reaction of 2′-benzyloxy-3,4,4′-trimethoxychalkone epoxide (XIII)

2′-Benzyloxy-3,4,4′-trimethoxychalkone (XII). Compound XI[7] (4·2 g) was dissolved in dry acetone (250 ml) and refluxed with benzyl chloride (3·1 ml), KI (3 g) and K_2CO_3 (10 g) for 48 hr. The product crystallized from EtOH–ethyl acetate as pale yellow large hexahedral prisms (3·5 g), m.p. 123–124° no colour with ethanolic $FeCl_3$. (Found: C, 74·5; H, 6·4. $C_{25}H_{24}O_5$ requires: C, 74·2; H, 6·0%).

2′-Benzyloxy-3,4,4′-trimethoxychalkone epoxide (XIII). The above chalkone (XII, 2 g) in acetone (20 ml) and MeOH (8 ml) was treated with NaOHaq (8%, 2·4 ml) followed by H_2O_2 (30%, 2·4 ml). The epoxide (XIII) crystallized from MeOH as colourless needles and elongated prisms (1·8 g), m.p. 97–98°; ν_{max} 1665 cm^{-1} (C=O), 1260 cm^{-1} (C—O—C epoxide). (Found: C, 71·4; H, 5·9. $C_{25}H_{24}O_6$ requires: C, 71·4; H, 5·8%).

7,3′,4′-Trimethoxyisoflavone (*Cabreuvin*, XIV). The above chalkone epoxide (XIII, 1·5 g) was reacted with BF_3–etherate (1·5 ml) and worked up as in the case of the chalkone epoxide (V). The isoflavone (XIV) crystallized from ethyl acetate–light petroleum as colourless needles (0·2 g), m.p. 158–159° (lit.[5] 164°); λ_{max} 255 mμ (4·51) and 261 mμ (4·52). (Found: C, 69·0; H, 5·3. Calc. for $C_{18}H_{16}O_5$: C, 69·2; H, 5·2%).

Reactions of 2′-benzyloxy-3,4,3′,4′-tetramethoxychalkone epoxide (XVI)

(*i*) *With ethereal hydrogen chloride* (*formation of 2-benzyloxy-3,4-dimethoxyphenyl-β-chloro-α-hydroxy-β-3,4-dimethoxyphenyl ethyl ketone*). The chalkone epoxide prepared from 2′-benzyloxy-3,4,3′,4′-tetramethoxychalkone[8] could not be crystallized but its identity was proved by conversion to the corresponding chlorohydrin by treatment with ice-cold ethereal HCl (2·5 ml) and shaking the solution for 5 min. The chlorohydrin crystallized from benzene-light petroleum as colourless stout rhombohedral prisms (0·2 g), m.p. 117–118°; λ_{max} 279 mμ (4·0); ν_{max} 3600 cm^{-1} (OH), 1665 cm^{-1} (C=O). (Found: C, 64·1; H, 5·9. $C_{26}H_{27}O_7Cl$ requires: C, 64·1; H, 5·5%).

(*ii*) *With boron trifluoride etherate* (*formation of 7,8,3′,4′-tetramethoxyisoflavone*, XVII). Treatment of the above epoxide (XV, 1·5 g) in benzene with BF_3-etherate and crystallization of the product from MeOH gave XVII as almost colourless needles (0·3 g), m.p. and mixed m.p. with an authentic sample[8] 164–165°; λ_{max} 254 mμ (4·17); ν_{max} 1640 cm^{-1} (C=O).

2′-Benzyloxy-2,4′-dimethoxychalkone. 2′-Hydroxy-2,4′-dimethoxychalkone[9] (6·0 g) in dry acetone

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[7] V. R. Shah, C. G. Joshi and A. B. Kulkarni, *Chem. & Ind.* 1062 (1955).

[8] L. R. Row and C. V. R. Sastry, *Tetrahedron* **19**, 1371 (1963).

[9] S. von Kostanecki and A. V. Szlagier, *Ber. Dtsch. Chem. Ges.* **37**, 4156 (1904).

(100 ml) was refluxed with benzyl chloride (6·5 ml), K_2CO_3 (21 g) and KI (5 g) for 24 hr. The product crystallized from EtOH–ethyl acetate as pale yellow needles (6·5 g), m.p. 118–119°; it gave no colour with ethanolic $FeCl_3$. (Found: C, 76·9; H, 6·1 $C_{24}H_{22}O_4$ requires: C, 77·0; H, 5·9%).

2′-Benzyloxy-2,4′-dimethoxychalkone epoxide. The above chalkone (4 g) was oxidized in acetone (40 ml) and MeOH (16 ml) with H_2O_2 (30%, 6·5 ml) and NaOHaq (8%, 6·5 ml) The epoxide crystallized from ethyl acetate–light petroleum as colourless needles (3·8 g), m.p. 91–92°. (Found: C, 73·3; H, 5·9. $C_{24}H_{22}O_5$ requires: C, 73·8; H, 5·7%).

2′-Benzyloxy-2,4,4′-trimethoxychalkone was prepared from 2′-hydroxy-2,4,4′-trimethoxychalkone[10] (5·6 g) using acetone (300 ml), benzyl chloride (5 ml), K_2CO_3 (20 g) and KI (5 g) as described earlier. It crystallized from ethyl acetate as pale yellow stout rectangular prisms and tablets (5·8 g), m.p. 162–163°, no colour with ethanolic $FeCl_3$. (Found: C, 73·7; H, 6·0 $C_{25}H_{24}O_5$ requires: C, 74·2; H, 6·0%).

2′-Benzyloxy-2,4,4′-trimethoxychalkone epoxide. As epoxidation was more difficult, modified conditions were employed: The chalkone (2 g) dissolved in acetone (130 ml) and MeOH (20 ml) was treated with a mixture of H_2O_2 (30%, 3·0 ml) and NaOHaq (8%, 3·0 ml). The mixture was shaken and brought to its b.p. occasionally during 1 hr and then left at room temp. After 2 hr, it was again treated with a mixture of H_2O_2 (30%; 1·5 ml) and NaOHaq (8%; 1·5 ml) and left overnight. Dilution with water gave the epoxide which crystallized from MeOH as elongated rectangular prisms (1·8 g), m.p. 111–112°. (Found: C, 71·1; H, 5·8. $C_{25}H_{24}O_6$ requires: C, 71·4; H, 5·7%).

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[10] S. von Kostanecki, V. Lampe and S. Triulzi, *Ber. Dtsch. Chem. Ges.* 92 (1906).