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CHALCONE DIHALIDES—V

ON THE ACID CATALYSED CYCLIZATION OF 4,6′-DIALKOXYCHALCONE DIBROMIDES TO 3-BROMOFLAVANONES

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Abstract—It is shown that the action of acetic acid on 2′-acetoxy-4,6′-dimethoxychalcone dibromide results in deacetylation, debromination of the side-chain, and nuclear halogenation rather than in elimination of hydrogen bromide to form an α-bromochalcone. The generality of the dehalogenation of the α,β-dibromo ketone in acetic acid and its relation to the ortho steric effect are discussed.

It has been proposed[1] that 2′-hydroxychalcone dihalides of class 2A, i.e. those with a 6′-alkoxyl substituent, may cyclize to flavones and/or aurones via an α-halogeno-chalcone in the base catalysed Emilewicz–von Kostanecki reaction. A serious objection to this proposal is the fact that the one such α-halogeno-2′-hydroxychalcone (**5**) to be studied[2,3] was found to be stable in base.

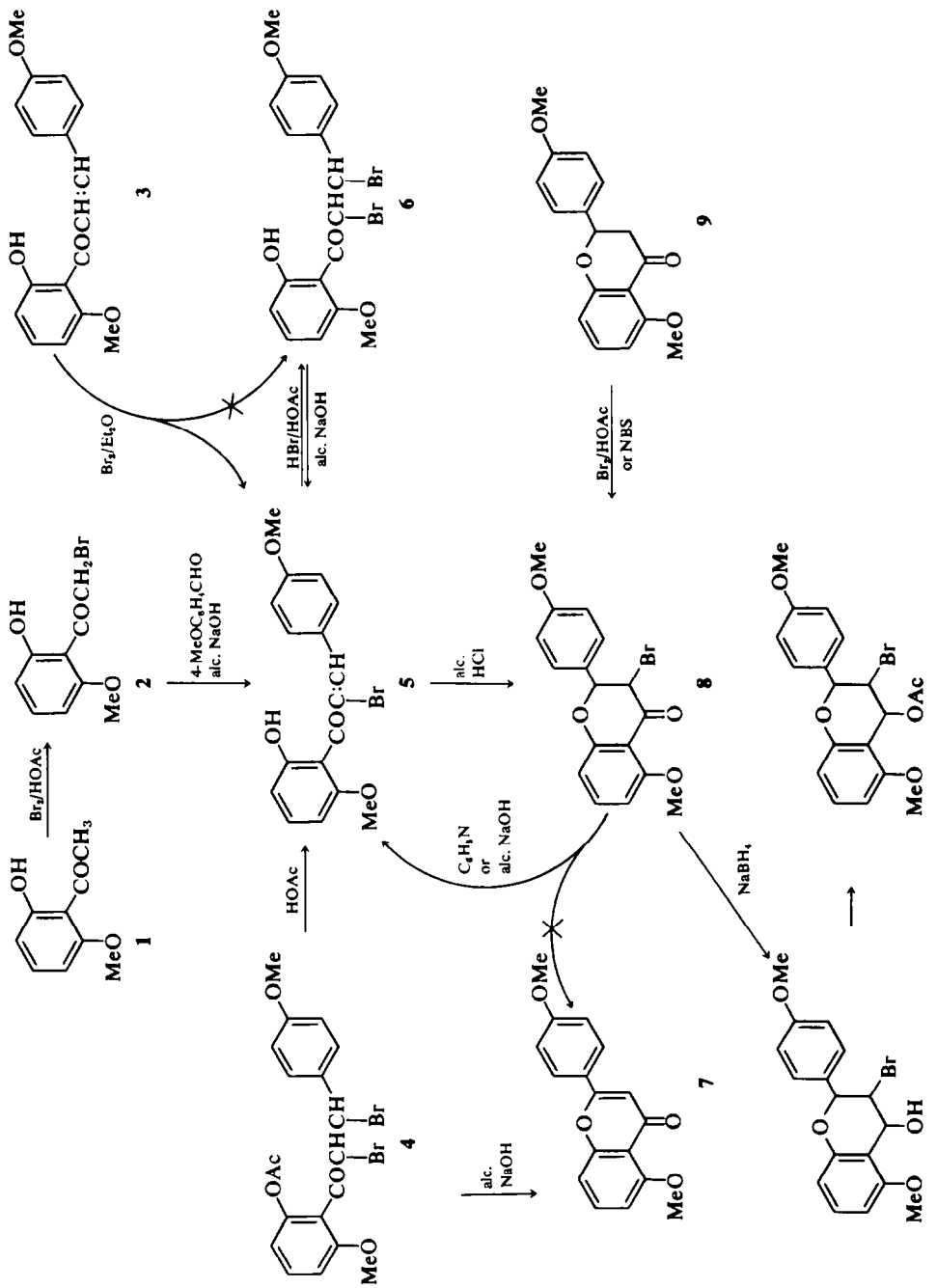
In 1956 Pendse[2] reported that 2′-acetoxy-4,6′-dimethoxychalcone dibromide (**4**) is converted by acetic acid into α-bromo-2′-hydroxy-4,6′-dimethoxychalcone (**5**) which, while stable in alkali, is cyclized by alcoholic hydrochloric acid to an epimer of 3-bromo-4′,5-dimethoxyflavanone (**8**). This synthesis of the epimer was repeated in 1970 by Mahajan *et al*[3] in their work on the stereospecific synthesis of 3-halogeno-flavanones. Like the previous finding[2] with alcoholic alkali, they observed that this 3-bromoflavanone (**8**) was reconverted into the α-bromochalcone (**5**) by pyridine.

The unexpected stability of this α-bromo-2′-hydroxychalcone (**5**) in base and its surprising formation—instead of 4′,5-dimethoxyflavone (**7**)—from the 3-bromoflavanone (**8**) led us to repeat the synthesis of the latter by Pendse's alternative method of brominating 2′-hydroxy-6′-methoxyacetophenone (**1**) in acetic acid, condensing the resulting 2-bromo-2′-hydroxy-6′-methoxyacetophenone (**2**) with anisaldehyde, and cyclizing the product, α-bromo-2′-hydroxy-4,6′-dimethoxychalcone (**5**) to the 3-bromoflavanone (**8**).

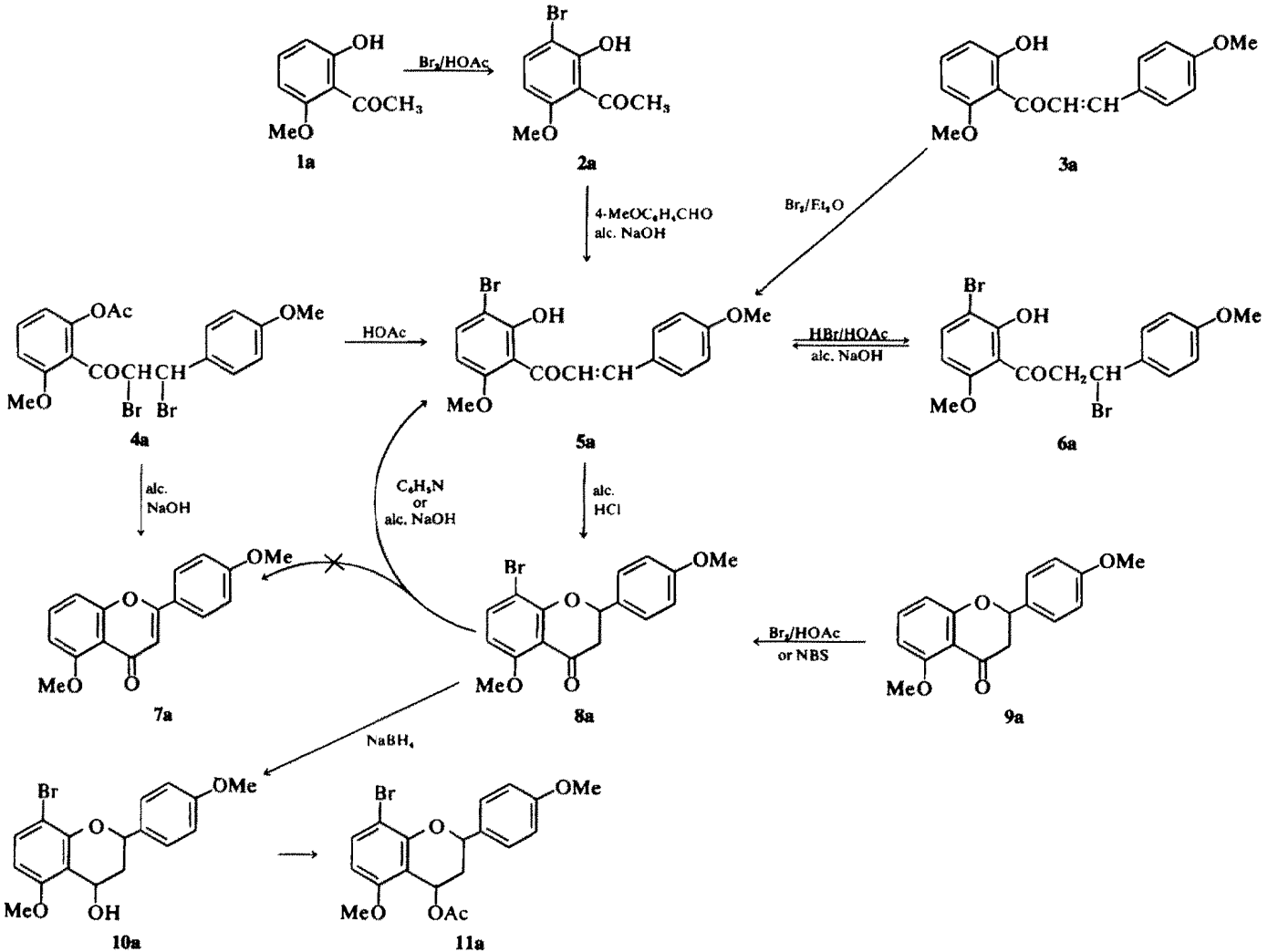
It is known[4] that bromination of 2′-hydroxy-6′-methoxyacetophenone (**1a**) in chloroform gives 3′-bromo-2′-hydroxy-6′-methoxyacetophenone (**2a**). We have had occasion[5] to repeat this bromination in both acetic anhydride and 80% acetic acid—with the same result. It has been observed,[6] however, that glacial acetic acid (as used by Pendse[2]) promotes side chain bromination of 2′-hydroxyacetophenones but when we now brominated 2′-hydroxy-6′-methoxyacetophenone (**1a**) in this solvent we again obtained only the nuclear brominated acetophenone (**2a**).

Although its m.p. (Table 1) was 3° below that recorded[2] for 2-bromo-2′-hydroxy-6′-methoxyacetophenone (**2**), we believe that it is the same compound as that obtained by Pendse. When condensed with anisaldehyde it gave 3′-bromo-2′-hydroxy-4,6′-dimethoxychalcone (**5a**), the physical properties of which (Table 1) are comparable with those recorded[2] for α-bromo-2′-hydroxy-4,6′-dimethoxychalcone (**5**). Cyclization of the 3′-bromochalcone (**5a**) under the conditions reported[2] for the cyclization of the supposed α-bromochalcone (**5**) gave 8-bromo-4′,5-dimethoxyflavanone (**8a**) with physical properties comparable to those recorded[2,3] for an epimer of 3-bromo-4′,5-dimethoxyflavanone (**8**).

We suggest, therefore, the assignment of a nuclear rather than of a side chain brominated structure to the product (**5a**) resulting from treatment of 2′-acetoxy-4,6′-dimethoxychalcone dibromide (**4a**) with acetic acid. Besides eliminating the difficulties of having an α-bromochalcone stable in alkali and a 3-bromoflavanone not forming a flavone under similar conditions, it also accounts (Scheme 2) for other difficulties in the previous work (Scheme 1) such as (i) the inability of 2′-hydroxy-4,6′-dimethoxychalcone dibromide (**6**) to react like its acetate (**4**) and undergo the Emilewicz–von Kostanecki reaction (**4** → **7**), (ii) the failure of a 2-bromo-2′-hydroxyacetophenone (**2**) to form[7] either a flavanol or an aurone



SCHEME 1. Structures previously assigned to products related to 2'-acetoxy-4,6'-dimethoxychalcone dibromide (4).



SCHEME 2. New assignment of structures to products related to 2′-acetoxy-4,6′-dimethoxychalcone dibromide (**4a**).

Table 1. Physical data for pairs of compounds now believed to be identical

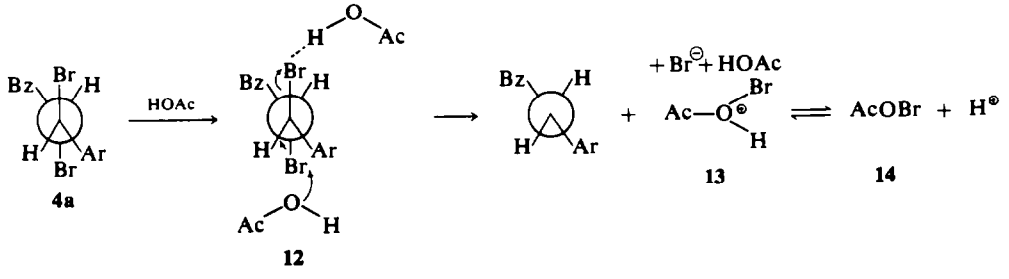
Product		M.p. (°C)	Physical characteristics
3′-Bromo-2′-hydroxy-6′-methoxyacetophenone[a,4]	(2a)	102–3[b]	Lime prisms from ethanol; NMR spectrum:[c] 7·35 Ac, 3·65 5′-H, 2·40 4′-H, −4·04 OH
"2-Bromo-2′-hydroxy-6′-methoxyacetophenone"	(2)	106[2]	Crystals from alcohol[2]
3′-Bromo-2′-hydroxy-4,6′-*dimethoxychalcone*[a]	(5a)	129[b]	Red needles from acetic acid; NMR spectrum:[c] 6·10 4-OMe, 6·02 6′-OMe, 3·56 5′-H, 2·99 3,5-H, 2·33 4′-H, 2·30 2,6-H, 2·16 β-H, 2·11 α-H, −4·10 OH
"α-Bromo-2′-hydroxy-4,6′-dimethoxychalcone"	(5)	132[2]	Red needles from acetic acid[2]
8′-*Bromo*-4′,5-*dimethoxyflavanone*[a]	(8a)	153–4[b]	Colourless needles from ethanol; NMR spectrum:[c,d] 7·04 3-H_{eq}, 6·91 3-H_{ax}, 6·14 4′-OMe, 6·06 5-OMe, 4·46 2-H_{ax}, 3·47 6-H, 2·98 3′,5′-H, 2·49 2′,6′-H, 2·30 7-H, $J_{2,3(ax)}$ 12·7, $J_{2,3(eq)}$ 2·6, J_{gem} −16·2
"3-Bromo-4′,5-dimethoxyflavanone"	(8)	154[2,3]	Colourless needles from ethanol[3]

[a]Synthesised as described[2] for the compound immediately below; [b]taken with a Kofler hot-stage apparatus; [c]obtained at 60 MHz with a Perkin-Elmer R12 spectrometer, in $CDCl_3$, with TMS as internal reference, chemical shifts in τ-values, coupling constants in Hz; [d]the "deceptively-simple" spectrum of the heterocyclic-ring protons was analysed using the computer program NMRIT.[10]

when condensed with an aromatic aldehyde, and (iii) the non-occurrence of nuclear halogenation in the bromination of 4′,5-dimethoxyflavanone (**9**) and 2′-hydroxy-4,6′-dimethoxychalcone (**3**).

It is well established[3,8] that chalcone dihalides of class 2B, i.e. those with a 2- or 4-alkoxyl substituent, cyclize in acetic acid to *trans*-3-halogenoflavanones. The exception here noted is possibly general for those dihalides[2,3,9] that also have a 6′-alkoxyl substituent. The ortho steric effect of this substituent on phenyl–carbonyl conjugation would facilitate the removal of Br^+ from the α-position while the other alkoxyl group, in the 4-position, enables the elimination of the β-bromine atom as Br^-. It is likely that this elimination of bromine occurs by an E2 mechanism; in which case its *anti*-elimination is favoured over similar elimination of hydrogen bromide by the lack of benzoylphenyl eclipsing effects in the transition state (**12**), and by the acid solvent.

While it is conceivable that the bromine cation is then present in the solvent as the conjugate acid of acetyl hypobromite (**13**) or as the hypobromite itself (**14**), no such particularly reactive halogenating agents are required for the subsequent bromination of the 3′-position of the chalcone if the latter is now deacetylated.



4a 12 13 14

REFERENCES

[1]Part IV. J. A. Donnelly, H. J. Doran and J. J. Murphy, *Tetrahedron* **29**, 1037 (1973)
[2]H. K. Pendse, *Rasayanam* **2**, 131 (1956)
[3]P. Y. Mahajan, M. S. Kamat and A. B. Kulkarni, *Indian J. Chem.* **8**, 310 (1970)
[4]P. E. McCusker, E. M. Philbin and T. S. Wheeler, *J. Chem. Soc.* 2374 (1963)
[5]J. J. Beirne, A. M. Coyle and J. A. Donnelly, *Tetrahedron* **26**, 3809 (1970)
[6]N. P. Buu-Hoi, N. D. Xuong and D. Lavit, *J. Chem. Soc.* 1034 (1954)
[7]J. E. Gowan, P. M. Hayden and T. S. Wheeler, *Ibid.* 862 (1955) and refs. therein
[8]J. W. Clark-Lewis, T. M. Spotswood and L. R. Williams, *Aust. J. Chem.* **16**, 107 (1963); H. K. Pendse and S. D. Limaye, *Rasayanam* **2**, 90 (1955)
[9]K. R. Chandorkar, D. M. Phatak and A. B. Kulkarni, *J. Sci. Ind. Res. India* **21**, 24 (1962); P. Y. Mahajan, M. S. Kamat and A. B. Kulkarni, *Indian J. Chem.* **6**, 55 (1968)
[10]J. D. Swalen, *Computer Programs for Chemistry* (Edited by D. F. Detar) p. 54. W. A. Benjamin, Inc., New York (1968)