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FLAVONE FORMATION IN THE WHEELER AURONE SYNTHESIS

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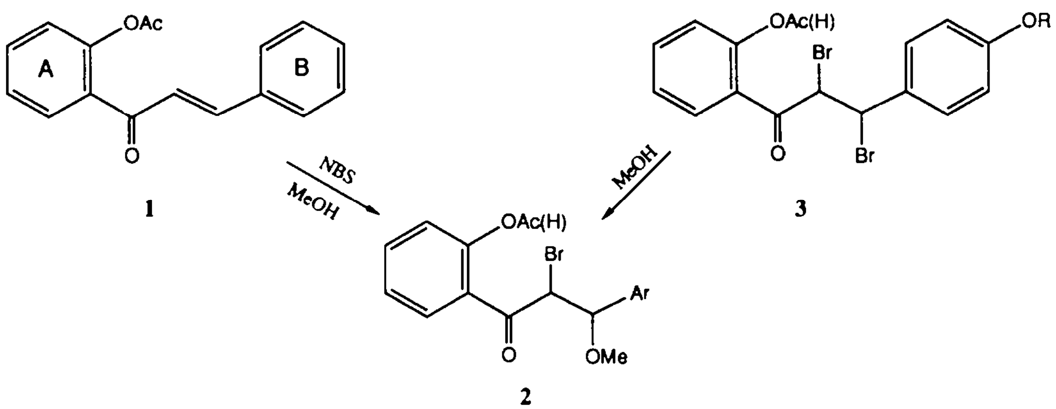
Abstract - *Dihydrochalcones, formed by bromomethylation of the side-chain of 2'-acetoxychalcones, were found to produce minor quantities of flavones as well as the major product, aurones, when cyclized by aqueous ethanolic sodium hydroxide. The yields of flavone increased with increasing base concentration. The optimum concentration of hydroxide for aurone formation was below 1% . Greatly diminished yields of O-heterocycles were obtained when a nitro substituent was introduced para to the cyclizing 2'-oxy function.*

It was shown[1] in 1979 that cyclizable α-bromo-β-methoxydihydrochalcones **2** are generally available from the reaction of 2'-acetoxychalcones **1** with *N*-bromosuccinimide (NBS) in methanol. Previously, only those with an *ortho* or *para* activating group in the B-ring were known - due to the ease with which the corresponding chalcone dibromide **3** underwent alcoholysis at the β-position. Except for those α-bromo-β-methoxydihydrochalcones di-*ortho*-substituted in the A-ring (which form[1] mainly flavone epoxides), these dihydrochalcones are cyclised by aqueous alcoholic alkali to aurones - the Wheeler aurone syntheses;[2] this is probably the most convenient method of synthesising these natural products. Bhide *et al*[3] have observed that the Wheeler reaction of B-ring activated dihydrochalcones may give products other than aurones - mainly flavones and 1,3-diketones - when certain bases and solvents are used. The results are here reported of a study of the heterocycles formed by the cyclization of a series of dihydrochalcones, each substituted in a position *meta* to the side-chain to minimise electronic effects on its leaving groups.



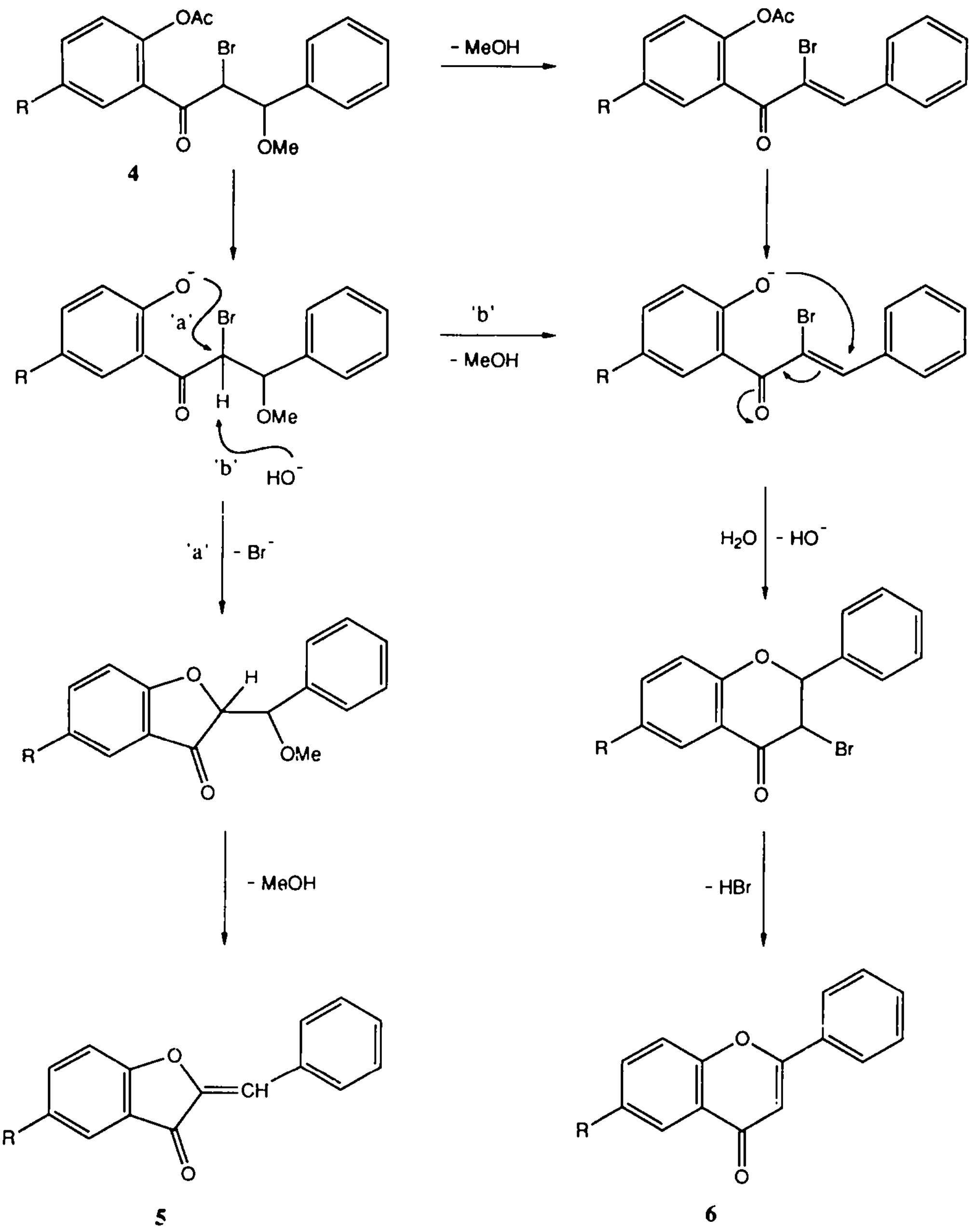
The Wheeler aurone synthesis is complimentary to the Emilewicz-von Kostanecki reaction[4] of chalcone dibromides which produce flavones, the naturally occurring six-membered *O*-heterocycles. For comparison purposes, therefore, reaction conditions were chosen which were closely similar to those reported[5] for a study of the latter reaction. Essentially, aqueous sodium hydroxide, of concentrations from 0.2M to 10.0M, was added to a solution or suspension of *ca* 6.5×10^{-5} moles of dihydrochalcone in a constant volume of methanol. The resulting cyclized products were examined by liquid chromatography. The results were given in Table.

It can be seen that, although aurones are the predominant product of this reaction (except at the highest concentration of added base), nevertheless, as the concentration of base was increased so too did the yield of flavones; there was a corresponding decrease in aurone production. The total yield of heterocycles decreased steadily with increasing base concentration, presumably due to base-initiated molecular fragmentation. For aurone production, the optimum base concentration in the overall reaction mixture was 0.5-1%, far lower than that generally employed (5%, approx.) in the Emilewicz - von Kostanecki flavone synthesis. 2'-Acetoxy-α-bromo-β-methoxydihydrochalcone **4a**, the only one of these dihydrochalcones previously studied,[1] has not been reported to yield flavone **6a**. However, it is now established that flavones are a general by-product of the Wheeler aurone synthesis and the phenomenon is not confined to the B-ring activated systems studied by Bhide *et al*[3].

While there is no obvious trend in the formation of either class of heterocycle related to the electronic characteristics of the various substituents, a nitro group *para* to the 2'-oxy substituent greatly diminishes cyclization in general; probably by drastically reducing the nucleophilicity of the incipient 2'-phenoxide ion. The lack of a simple trend may be due to deacetylation and side-chain elimination occurring contemporaneously and with different electronic requirements from the 5'-substituent. The masking of the 2'-phenoxide by acetylation was necessary to prevent nuclear bromination at the bromomethoxylation stage.

It is proposed (Scheme 1) that the formation of aurone **5** is the result of cyclosubstitution (path 'a') of phenoxide, resulting from hydrolysis of the acetate group, for the good leaving group, bromide. Flavone **6**

Scheme 1



a: R = H

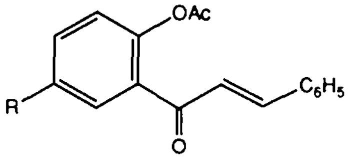
b: R = Me

c: R = Cl

d: R = NO_2

formation occurs (path 'b') *via* elimination of methanol from the side-chain by the intermolecular reaction of substrate with base and is, as observed, favoured by increasing base concentration.

The α-bromo-β-methoxydihydrochalcones **4a-d** were synthesised by the reaction of NBS with the corresponding 2'-acetoxychalcones **7** in methanol, usually for several days. The formation of 2'-acetoxy-α-bromo-β-methoxy-5'-nitrodihydrochalcone **4d** required an excess of NBS and slight warming; too large an excess of NBS gave 2'-acetoxy-5'-nitrochalcone dibromide **8** (R = NO_2).



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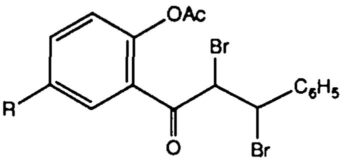

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6-Methylflavone **6b** and 6-chloroflavone **6c**, required for use as external references for liquid chromatography, were synthesised by the Emilewicz-von Kostanecki cyclization of 2'-acetoxy-5'-methylchalcone dibromide **8** (R = Me) and 2'-acetoxy-5'-chlorochalcone dibromide **8** (R = Cl), respectively, while flavone[6] **6a** and 6-nitroflavone[7] **6d** were prepared as previously reported. 5-Methylaurone **5b**, 5-chloroaurone **5c**, and 5-nitroaurone **5d**, for use as external references, were obtained by the Wheeler cyclization of the corresponding α-bromo-β-methoxydihydrochalcones **4b-d**. Aurone **5a** was similarly prepared.[1] 5-Nitroaurone **5d** could not be purified by crystallization until the admixed 6-nitroflavone **6d** was removed by chromatography.

Table. Yields (%) of aurones (A) **5** and flavones (F) **6** from the reaction of α-bromo-β-methoxydihydrochalcones **4** with base.

Chalcone 4	R=H		R=Me		R=Cl		R=NO_2	
Conc. of added NaOH	A	F	A	F	A	F	A	F
1.0M	96	4	74	6	67	16	23	22
2.0M	85	6	78	7	54	34	15	11
3.0M	61	8	70	8	48	24	18	7
4.0M	63	11	70	12	21	23	22	6
5.0M	51	25	70	21	19	37	22	7
10.0M	14	47	21	26	15	38	24	8

Experimental

Melting points were determined with a Reichert Thermovar hot-block and are uncorrected. Nmr spectra were recorded at 270 MHz on a JEOL JNM-GX FT Nmr spectometer in $CDCl_3$ solutions containing Me_4Si as an internal standard. Merck silica gel PF $_{254+366}$ was used for preparative thin layer chromatography (PLC). For liquid chromatography, a Waters Associates HPLC fitted with a μ-Bondapak (100 mm x 8 mm) C_{18} reverse phase cartridge, connected to an LDC/Milton Roy C1-108 integrator using a fixed wavelength (214 mn) detector and external standards. $MeOH/H_2O$ (80:20) was employed as the mobile phase at a flow rate of 1 ml/min.

2'-Acetoxy-α-bromo-β-methoxydihydrochalcone and related compounds

This dihydrochalcone[1] **4a**, flavone[6] **6a**, and the aurone[1] **5a** were prepared as previously reported.

Cyclization of α-bromo-β-methoxydihydrochalcones (Table)

A suspension of the 2'-acetoxy-α-bromo-β-methoxydihydrochalcone **4** (*ca* 6.5×10^{-5} mole) in MeOH (5 ml) was stirred at 25°C for 15 min. Aqueous NaOH (1 ml), of the molarities shown, was added and the yellow solution was stirred at 25°C for 1 h. H_2O (20 ml) and sufficient dilute HCl to acidify the solution were added. The mixture was then extracted with $CHCl_3$ (5 x 10 ml). The extract was washed with water (1 x 10 ml), dried over anhydrous $MgSO_4$, and evaporated to dryness. The residual oil was examined by liquid chromatography for its aurone **5** and flavone **6** content.

2'-Acetoxy-α-bromo-β-methoxy-5'-methyldihydrochalcone

Anhydrous NaOAc (4.0 g) was added to a solution of 2'-hydroxy-5'-methylchalcone (2.0 g) in Ac_2O (10 ml), heated on a steambath for 2 h, and poured into H_2O (50 ml). The precipitate gave 2'-acetoxy-5'-methylchalcone **7** (R = Me), pale yellow crystals (1.0 g), m.p. 52-54°C (EtOH). Hmr δ 2.22 (s, Ac), 2.41 (s, Me), 7.04-7.62 (m, 10 H). Found: C, 77.35; H, 5.87; $C_{18}H_{16}O_3$ requires: C, 77.12; H, 5.75%.

NBS (0.46 g) was added to a solution of the acetate **7** (R = Me) (0.61 g) in MeOH (30 ml). After 4 days, the precipitate was collected and gave 2'-acetoxy-α-bromo-β-methoxy-5'-methyldihydrochalcone **4b**, white needles (0.45 g), m.p. 110-111°C (MeOH). Hmr δ 2.36 (s, Ac), 2.41 (s, CH_3Ar), 3.19 (s, OMe), 4.77 (d, β-H, J 10Hz), 5.04 (d, α-H, J 10 Hz), 7.05 (d, 3'-H, J 8 Hz), 7.35-7.44 (m, 6 H), 7.61 (d, 6'-H, J 2 Hz). Found: C, 58.10; H, 4.83; Br, 20.28. $C_{19}H_{19}BrO_4$ requires: C, 58.33; H, 4.89; Br, 20.42%.

Aqueous NaOH (2.0 M; 3 ml) was added to a suspension of the dihydrochalcone **4b** (0.2 g) in MeOH (10 ml), stirred for 1 h, and diluted with H_2O (20 ml). The precipitate gave 5-methylaurone[8] **5b** (0.08 g), m.p. 118-119°C (MeOH). Hmr δ 2.48 (s, Me), 6.84 (s, CHPh), 7.10-7.92 (m, 8 H).

Br_2 (0.31 g) in $CHCl_3$ (10 ml) was added to a solution of the acetoxychalcone **7** (R = Me) (0.52 g) in $CHCl_3$ (20 ml). The oil obtained by removal of the solvent next day, gave 2'-acetoxy-5'-methylchalcone dibromide **8** (R = Me) white needles (0.48 g), m.p. 124-125°C (MeOH). Hmr δ 2.41 (s, Ac), 2.44 (s, Me), 5.57 (d, α-H, J 11 Hz), 5.77 (d, β-H, J 11 Hz), 7.10 (d, 3'-H, J 8 Hz), 7.37-7.50 (m, 6 H), 7.74 (d, 6'-H, J 2 Hz). Found: C, 49.02; H, 3.59; Br, 35.90. $C_{18}H_{16}Br_2O_3$ requires: C, 49.12; H, 3.66; Br, 36.31%.

Aqueous NaOH (2.0 M; 2 ml) was added to a suspension of the chalcone dibromide **8** (R = Me) (0.15 g) in MeOH (5 ml). After 1 h, H_2O (20 ml) was added and the resulting precipitate gave 6-methylflavone[9] **6b**, yellow needles (0.07 g), m.p. 122-123°C. Hmr δ 2.47 (s, Me), 6.82 (s, 3-H), 7.45-8.03 (m, 8 H).

Anhydrous NaOAc (8.0 g) was added to a solution of 5'-chloro-2'-hydroxychalcone (6.0 g) in Ac_2O (30 ml), heated on a steambath for 2 h, and poured into H_2O (100 ml). The precipitate gave 2'-acetoxy-5'-chlorochalcone[10], **7** (R = Cl), yellow needles (6.36 g), m.p. 100-101°C (EtOH). Hmr δ 2.22 (s, Ac), 7.11-7.62 (m, 9 H), 7.65 (d, 6'-H, J 3 Hz). Found: C, 67.89; H, 4.38; Cl, 11.60. $C_{17}H_{13}ClO_3$ requires: C, 67.89; H, 4.36; Cl, 11.79%.

NBS (1.1 g) was added to a solution of the acetoxychalcone **7** (R = Cl) (1.5 g) in MeOH (50 ml). The oil, obtained by removal of the solvent after 3 days, gave 2'-acetoxy-α-bromo-5'-chloro-β-methoxydihydrochalcone **4c**, white needles (1.45 g), m.p. 88-90°C (MeOH/H_2O). Hmr δ 2.37 (s, Ac), 3.19 (s, OMe), 4.74 (d, β-H, J 10 Hz), 4.96 (d, α-H, J 10 Hz), 7.14 (d, 3'-H, J 8 Hz), 7.42 (s, Ph), 7.53 (q, 4'-H, J 9 and 3 Hz), 7.78 (d, 6'-H, J 3 Hz). Found: C, 52.20; H, 3.86; Br, 19.78; Cl, 8.51. $C_{18}H_{16}BrClO_4$ requires: C, 52.52; H, 3.92; Br, 19.41; Cl, 8.61%.

The dihydrochalcone **4c** (0.2 g) in conc. HCl (1 ml) and MeOH (10 ml) was refluxed for 2 h. The precipitate obtained by the addition of H_2O, gave α-bromo-5'-chloro-2'-hydroxy-β-methoxydihydrochalcone, yellow granules (0.14 g), m.p. 108-109°C (EtOH). Hmr δ 3.20 (s, Me), 4.82 (d, β-H, J 10 Hz), 5.07 (d, α-H, J 10 Hz), 7.01 (d, 3'-H, J 9 Hz), 7.40-7.49 (m, 6 H), 7.73 (d, 6'-H, J 3 Hz), 11.90 (s, OH). Found: C, 51.69; H, 3.77; Br, 21.53; Cl, 9.29. $C_{16}H_{14}BrClO_3$ requires: C, 51.99; H, 3.82; Br, 21.62; Cl, 9.59%.

Aqueous NaOH (1.0 M; 2 ml) was added to a suspension of the acetoxydihydrochalcone **4c** (0.2 g) in MeOH (10 ml), stirred for 1 h, and diluted with H_2O (20 ml). The resulting precipitate gave 5-chloroaurone[11] **5c**, yellow needles (0.032 g), m.p. 163-164°C (EtOH). Hmr δ 6.93 (s, CHPh), 7.27-7.93 (m, 8 H).

Br_2 (0.53 g) in CCl_4 (20 ml) was added to a solution of 2'-acetoxy-5'-chlorochalcone **7** (R = Cl) (1.0 g) in CCl_4 (50 ml). The oil, obtained by removal of the solvent next day, gave 2'-acetoxy-5'-chlorochalcone dibromide **8** (R = Cl) white flakes (0.66 g), m.p. 113-114°C (EtOH). Hmr δ 2.42 (s, Ac), 5.54 (d, α-H, J 11 Hz), 5.71 (d, β-H, J 11 Hz), 7.19 (d, 3'-H, J 8 Hz), 7.35-7.50 (m, Ph), 7.58 (q, 4'-H, J 9 and 3 Hz), 7.90 (d, 6'-H, J 3 Hz). Found C, 44.31; H, 2.73; Br, 34.87; Cl, 7.43. $C_{17}H_{13}Br_2ClO_3$ requires: C, 44.34; H, 2.84; Br, 34.70; Cl, 7.70%.

Aqueous NaOH (2.0 M; 2 ml) was added to a suspension of the chalcone dibromide **8** (R = Cl) (0.15 g) in EtOH (10 ml), stirred for 1 h, and diluted with H_2O (20 ml). The resulting precipitate gave 6-chloroflavone[12] **6c**, yellow needles (0.08 g), m.p. 183-184°C (EtOH). Hmr δ 6.83 (s, 3-H), 7.51-7.93 (m, 7 H), 8.20 (d, 5-H, J 3 Hz).

2'-Acetoxy-α-bromo-β-methoxy-5'-nitrodihydrochalcone and related compounds

Anhydrous NaOAc (2.0 g) was added to a solution of 2'-hydroxy-5'-nitrochalcone (1.0 g) in Ac_2O (10 ml), heated on a steambath for 2 h, and poured into water (50 ml). The precipitate gave 2'-acetoxy-5'-nitrochalcone[13] **7** (R = NO_2), pale yellow needles (0.84 g), m.p. 117-119°C (EtOH). Hmr δ 2.28 (s, Ac), 7.17 (d, α-H, J 16 Hz), 7.39 (d, 3'-H, J 9 Hz), 7.41-7.62 (m, Ph), 7.63 (d, β-H, J 16 Hz), 8.41 (q, 4'-H, J 9 and 3 Hz), 8.56 (d, 6'-H, J 3 Hz).

NBS (0.33 g) was added to a solution of the acetoxychalcone **7** (R = NO_2) (0.44 g) in MeOH (60 ml), stirred for 24 h at 40°C, diluted with H_2O, and extracted with Et_2O. The ether extract was washed with H_2O, dried, and evaporated to dryness. The resulting oil gave 2'-acetoxy-α-bromo-β-methoxy-5'-nitrodihydrochalcone **4d**, white crystals (0.3 g), m.p. 97-99°C (Et_2O/light petroleum, 50:50). Hmr δ 2.42 (s, Ac), 3.21 (s, OMe), 4.76 (d, β-H, J 10 Hz), 4.98 (d, α-H, J 10 Hz), 7.38-7.44 (m, 6 H), 8.42 (q, 4'-H, J 9 and 3 Hz), 8.68 (d, 6'-H, J 3 Hz). Found: C, 50.83; H, 3.81; Br, 19.19; N, 3.50. $C_{18}H_{16}BrNO_6$ requires: C, 51.20; H, 3.82; Br, 18.92; N, 3.32%.

Aqueous NaOH (2 M; 2 ml) was added to a suspension of the dihydrochalcone **4d** (0.6 g) in MeOH (5 ml), stirred for 1 h, and diluted with H_2O (20 ml). The precipitate was fractionated by PLC. The fraction with the larger R_f value gave 5-nitroaurone **5d**, yellow needles (0.025 g), m.p. 168-170°C (EtOH). Hmr δ 6.53 (s, CHPh), 7.35-7.45 (m, 6 H), 8.20 (q, 6-H, J 9 and 2.5 Hz), 8.42 (d, 4-H, J 2.5 Hz). Found: C, 67.92; H, 3.33; N, 5.14. $C_{15}H_9NO_4$ requires: C, 67.42; H, 3.39; N, 5.24%. The other fraction gave 6-nitroflavone[7] **6d**, yellow plates (0.02 g), m.p. 190-192°C (EtOH).

References

1. J.A. Donnelly, M.J. Fox, and T.C. Sharma, *Tetrahedron*, **35**, 875 (1979).
2. See reference 2 of reference 1.
3. G.V Bhide, K.R. Chandorkar, H.K. Pendse, and S.D. Limaye, *Rasayanam*, **2**, 135 (1956).
4. T. Emilewicz and S. von Kostanecki, *Chem. Ber.*, **31**, 696 (1898); J.A. Donnelly and H.J. Doran, *Tetrahedron Lett.*, 4083 (1974).
5. J.A. Donnelly and H.J. Doran, *Tetrahedron*, **31**, 1565 (1975).
6. A.M. Warriar, A.P. Khanolkar, W.A. Hutchins, and T.S. Wheeler, *Current Sci.*, 475 (1937).
7. G.S. Chhaya, P.L. Trivedi, and G.V. Jadhav, *J. Univ. Bombay*, **25**, 8 (1957).

8. J.E. Gowan, P.M. Hayden, and T.S. Wheeler, *J. Chem. Soc.*, 862 (1955).

9. O. Dann and G. Mylius, *Liebigs Ann.*, **587**, 1 (1954).

10. N.M. Shah and S.R. Parikh, *J. Indian Chem. Soc.*, **36**, 726 (1959).

11. T.P.C. Mulholland, H.D. Preston, and D.T. Rosevear, *J. Chem. Soc.*, 4939 (1965).

12. S. Ruhemann, *Chem. Ber.*, **54**, 912 (1921).

13. L. Reichel and G. Hempel, *Liebigs Ann.*, **625**, 184 (1959).