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Isocoumarins : Part 4. Synthesis of 5,6-dimethoxy, 6,7-dimethoxy, 7,8-dimethoxy, 5,7-dimethoxy, 5,8-dimethoxy-3-methyl-isocoumarins and a new synthesis of (±)-6-methoxy mellein

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Abstract. *o*-Lithio 2,3- ; 3,4- ; 3,5- ; 2,5- and 2,4-dimethoxy-N-methyl-benzamides upon condensation with propylene oxide give corresponding dimethoxy-3-methyl-3, 4-dihydroisocoumarins. The method has been used to synthesise (±)-6-methoxy mellein. 3-Methyl-6,7-dimethoxy-3,4-dihydroisocoumarin has been synthesised by an acid catalysed cyclisation reaction. The dihydroisocoumarins have been dehydrogenated to respective isocoumarins.

Keywords. *o*-Lithio-N-methylbenzamides; dihydroisocoumarins; isocoumarins.

1. Introduction

The dihydroisocoumarins having a C_3-methyl group and $-OCH_3$ or $-OH$ substituent in the benzene ring are quite common in nature, e.g., mellein (Nishikawa 1933), reticulol (Mitscher *et al* 1964), (−) Kigelin (Govindachari *et al* 1971) (−)-5-methyl mellein (Ballio *et al* 1966), etc. Recently a new synthesis of methoxy-isocoumarins was developed (Narasimhan 1971; Bhide and Gupta 1977). We have explored this reaction further for the synthesis of various dimethoxy-isocoumarins. There are a few methods for the synthesis of methoxyisocoumarins (Bose and Chaudhury 1964, 1969; Banerjee and Chaudhury 1964). However these are all acid catalysed cyclisation methods and comprise several steps. (−)-6-Methoxy mellein is a naturally occurring phenolic dihydroisocoumarin isolated by Sondheimer (1957) from mouldy carrots (Sondheimer 1957). Slates *et al* (1967) have sythesised (±)-6-methoxy mellein in five steps starting with 5,7-dimethoxy-indanone. Logan and Newbold (1957) have also reported the synthesis of (±)-6-methoxy mellein methyl ether which comprises six steps. We now report a better two-step synthesis of racemic 6-methoxymellein.

In the present work lithiation reaction is the key step for the synthesis of various dimethoxydihydroisocoumarins. Hence it is necessary to mention an interesting aspect of lithiation reaction. Lithiation usually occurs ortho to the carboxyamide

group, irrespective of the position of methoxyl group (Narasimhan and Bhide 1971; Bhide and Gupta 1977). Thus lithiation of the amide I, can take place at two possible ortho positions, which can eventually give either VI or XXI. In the present work only one product, i.e., VI was isolated. Since XXI was not obtained by lithiation method, it became necessary to employ a conventional, longer sequence to synthesise XXI, by an acid catalysed cyclisation method as indicated in chart 2.

2. Results and discussion

The condensation of *o*-lithio derivatives of 2,3-; 3,4-; and 3,5-dimethoxy-N-methyl benzamides with propylene oxide smoothly gave corresponding 3-methyl-3, 4-dihydroisocoumarins in good yields. *o*-Lithio-2,5-dimethoxy-N-methylbenzamide upon condensation with propylene oxide gave two products, 3-methyl-5,8-dimethoxy-3,4-dihydroisocoumarin (IX) and a phenolic compound. The phenolic compound was shown to be (X), obtained by the selective (Anhy. $AlCl_3$) demethylation of (IX). The formation of phenolic compound (X) was rather surprising, however such type of demethylation during lithiation has been earlier observed (Narasimhan and Bhide 1971). *o*-Lithio-2,4-dimethoxy-N-methylbenzamide upon condensation with propylene oxide, followed by hydrolysis gave (±)-6-methoxy-mellein methyl ether (XI). The selective demethylation of (XI) gave (±)-6-methoxy-mellein (XII), identical in all respects with an authentic sample.

The dihydroisocoumarins were smoothly dehydrogenated to corresponding isocoumarins in good yields by the known procedure (Narasimhan and Bhide 1971). The structures of all the compounds have been supported by analysis and spectral data.

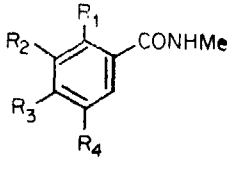
3. Experimental

For general remarks see Bhide (1977) in this series.

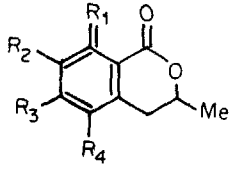
3.1. *Preparation of dimethoxy-N-methylbenzamides*

The dimethoxy-N-methylbenzamides were prepared by slowly adding the corresponding acid chloride to 33% methylamine solution at 0° C.

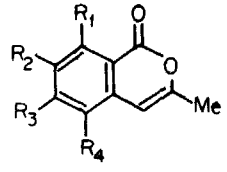
3,4-Dimethoxy-N-methylbenzamide (I), white needles from ethylacetate-hexane, m.p. 126–7° (Found : N, 7·03; $C_{10}H_{13}O_3N$ requires N, 7·18%). 2,3-Dimethoxy-N-methylbenzamide (II), white crystals from ethylacetate-hexane, m.p. 74° (Found : N, 7·10; $C_{10}H_{13}O_3N$ requires N, 7·18%). 3,5-Dimethoxy-N-methylbenzamide (III), white needles from ethylacetate-hexane, m.p. 115–16° (Found N, 7·32%, $C_{10}H_{13}O_3N$ requires N, 7·18%). 2,5-Dimethoxy-N-methylbenzamide (IV), b.p. 220–5° C (Found : N, 7·36; $C_{10}H_{13}O_3N$ requires N, 7·18%). 2,4-Dimethoxy-N-methylbenzamide (V), white needles from ethylacetate-hexane, m.p. 71° (Found : N, 7·06; $C_{10}H_{13}O_3N$ requires N, 7·18%).



I, $R_1 = R_2 = H$; $R_3 = R_4 = OMe$
II, $R_3 = R_4 = H$; $R_1 = R_2 = OMe$
III, $R_1 = R_3 = H$; $R_2 = R_4 = OMe$
IV, $R_2 = R_3 = H$; $R_1 = R_4 = OMe$
V, $R_2 = R_4 = H$; $R_1 = R_3 = OMe$



VI, $R_1 = R_2 = H$; $R_3 = R_4 = OMe$
VII, $R_3 = R_4 = H$; $R_1 = R_2 = OMe$
VIII, $R_1 = R_3 = H$; $R_2 = R_4 = OMe$
IX, $R_2 = R_3 = H$; $R_1 = R_4 = OMe$
X, $R_2 = R_3 = H$; $R_1 = OH$; $R_4 = OMe$
XI, $R_2 = R_4 = H$; $R_1 = R_3 = OMe$
XII, $R_2 = R_4 = H$; $R_1 = OH$; $R_3 = OMe$



XIII, $R_1 = R_2 = H$; $R_3 = R_4 = OMe$
XIV, $R_3 = R_4 = H$; $R_1 = R_2 = OMe$
XV, $R_1 = R_3 = H$; $R_2 = R_4 = OMe$
XVI, $R_2 = R_3 = H$; $R_1 = R_4 = OMe$

Chart 1

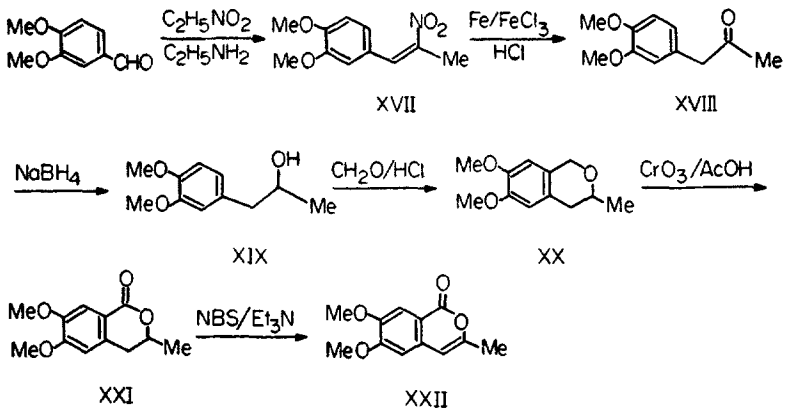


Chart-2

3.2. *Lithiation and condensation of lithio derivatives with Propylene oxide*

The following general procedure was used.

To a well stirred solution of dimethoxy-N-methylbenzamide (I to V), (5 g; 0·0256 mol), in dry THF (75 ml) was added, at room temperature *n*-BuLi (0·128 mol) in dry ether under N_2 atmosphere during 10 mins. The resulting red metalation mixture was then refluxed for 30 min. The metalation mixture upon condensation with propylene oxide (8·94 ml) in dry ether at 0° C, and alkaline hydrolysis work up as before (Narasimhan and Bhide 1971; Bhide and Shah 1980), gave the following 3-methyl-3,4-dihydroisocoumarins.

3.2a. 3-*Methyl*-5,6-*dimethoxy*-3,4-*dihydroisocoumarin* (VI). White needles, crystallised from ethylacetate-hexane (1·2 g), m.p. 105–7° (Found: C, 64·54; H, 6·10; $C_{12}H_{14}O_4$ requires C, 64·86, H, 6·30%); IR : 1710 cm^{-1} (δ lactone), 2960 cm^{-1} (CH_3 stretching), 820 cm^{-1} (two adjacent aromatic hydrogens); UV: 265, 328 nm (log ϵ 4·34, 3·18); NMR : δ 1·45 (3H, d, J = 7·0 Hz, $-CH_2-\underset{\underset{|}{-O}}{CH}-CH_3$), 2·9 (2H, 8 lines, the AB part of an ABX system, J_{AB} = 16 Hz, J_{AX} = 4 Hz, J_{BX} = 11 Hz), 3·8 and 3·9 (6H, two singlets, two $-OCH_3$ groups), 4·5 (1H, complex pattern of the X part of an ABX system $-CH_2-\underset{\underset{|}{-O}}{CH}-CH_3$), 6·85 (1H, d, J_{ortho} = 9·0 Hz, H_7), 7·8 (1H, d, J_{ortho} = 9·0 Hz, H_8).

3.2b. 3-*Methyl*-7,8-*dimethoxy*-3,4-*dihydroisocoumarin* (*VII*): White needles, crystallised from ether-hexane (500 mg), m.p. 85° (Found : C, 64·71; H, 6·54; $C_{12}H_{14}O_4$ requires C, 64·86; H, 6·30%); IR: 1720 cm^{-1} (δ-lactone), 2920 cm^{-1} (CH_3 stretching), 1370 cm^{-1} (CH_3 bending), 820 cm^{-1} (two adjacent aromatic hydrogens); UV : 220, 310 nm (log ϵ 4·8, 3·81); NMR : δ 1·45 (3H, d, J = 7·0 Hz,

$-CH_2-\underset{\underset{O}{|}}{CH}-CH_3$), 2·8 (2H, d, J = 7·0 Hz, benzylic $-CH_2-$), 3·85 and 3·95 (6H, two singlets, two-OCH_3 groups), 4·5 (1H, m, $-CH_2-\underset{\underset{O}{|}}{CH}-CH_3$), 6·9 (1H, d, J_{ortho} = 9·0 Hz, H_6), 7·2 (1H, d, J_{ortho} = 9·0 Hz, H_5).

3.2c. *3-Methyl-5,7-dimethoxy-3,4-dihydroisocoumarin* (*VIII*): White needles crystallised from ether-hexane (1·4 g), m.p. 102–3° (Found: C, 64·90; H, 6·20; $C_{12}H_{14}O_4$ requires C, 64·86; H, 6·30%); IR : 1720 cm^{-1} (δ -lactone), 2940 cm^{-1} (CH_3 stretching), 1355 cm^{-1} (CH_3 bending); UV : 253, 265, 300, 325 nm (log ϵ 2·91, 2·9, 3·06, 3·09); NMR : δ 1·5 (3H, d, J = 7·0 Hz, $-CH_2-\underset{\underset{O}{|}}{CH}-CH_3$), 2·8 (2H, 8 lines, the AB part of an ABX system J_{AB} = 17 Hz, J_{AX} = 4 Hz, J_{BX} = 11 Hz), 3·85 (6H, S, two $-OCH_3$ groups signal merged), 4·6 (1H, complex pattern of the X part of an ABX system $-CH_2-\underset{\underset{O}{|}}{CH}-CH_3$), 6·65 (1H, d, J_{meta} = 3·0 Hz, H_6), 7·15 (1H, d, J_{meta} = 3·0 Hz, H_8).

3.2d. *3-Methyl-5,8-dimethoxy-3,4-dihydroisocoumarin* (*IX*): White solid crystal lised from ether-hexane (800 mg), m.p. 85° (Found : C, 65·63; H, 6·15; $C_{12}H_{14}O_4$ requires C, 64·86; H, 6·30%); IR : 1710 cm^{-1} (δ-lactone), 2960 cm^{-1} (CH_3 stretching), 1340 cm^{-1} (CH_3 bending), 815 cm^{-1} (two adjacent aromatic hydrogens); UV : 220, 330 nm (log ϵ 4·82, 3·87); NMR : δ 1·5 (3H, d, J = 5·0 Hz, $-CH_2-\underset{\underset{O}{|}}{CH}-CH_3$), 2·9 (2H, 8 lines, the AB part of an ABX system J_{AB} = 13 Hz, J_{AX} = 3 Hz, J_{BX} = 9·0 Hz), 3·8 and 3·9 (6H, two singlets, two $-OCH_3$ groups), 4·5 (1H, complex pattern of the X part of an ABX system $-CH_2-\underset{\underset{O}{|}}{CH}-CH_3$), 6·85 and 7·05 (2H, two doublets, J_{ortho} = 7 Hz, H_6 and H_7).

3.2e. *3-Methyl-5-methoxy-8-hydroxy-3,4-dihydroisocoumarin. Phenolic compound* (*X*): White needles, crystallised from ether–hexane (250 mg), m.p. 83–5° (Found: 63·30; H, 5·94; $C_{11}H_{12}O_4$ requires C, 63·46; H, 5·76%), IR: 1695 cm^{-1} (δ-lactone-H-bonded), 2950 cm^{-1} (CH_3 stretching), 3100–3200 cm^{-1} (O–H stretching), UV: 250, 340 nm (log ϵ 3·82, 3·78); NMR : δ 1·5 (3H, d, J = 7·0 Hz, $-CH_2-\underset{\underset{O}{|}}{CH}-CH_3$), 2·8 (2H, 8 lines, the AB part of an ABX system J_{AB} = 17 Hz, J_{AX} = 4 Hz, J_{BX} = 11 Hz), 3·75 (3H, S, one $-OCH_3$ group), 4·55 (1H, complex pattern of the X part of an ABX system $-CH_2-\underset{\underset{O}{|}}{CH}-CH_3$), 6·7 (1H, d, J_{ortho} = 9·0 Hz, H_6) 7·0 (1H, d, J_{ortho} = 9·0 Hz, H_7).

Demethylation of (IX) : (IX) (100 mg) was refluxed with anhy. $AlCl_3$ in dry ether (20 ml) for 1 hr. The ether was evaporated and the excess of $AlCl_3$ was decomposed with dilute HCl. The reaction mixture was extracted with methylene chloride. Methylene chloride extract was washed with water and dried (Na_2SO_4). Removal of methylene chloride gave white solid compound. Crystallised from ether-hexane (50 mg). m.p.; mixed m.p. and TLC similar to (X).

3.2f. (±)-6-*Methoxymellein methyl ether (XI)*: White crystals from ether-hexane (100 mg), m.p. 103° (lit. m.p. 102–3·5°, Logan and Newbold 1957); (Found : C, 64·52; H, 6·13, $C_{12}H_{14}O_4$ requires C, 64·86; H, 6·30%); IR : 1720 cm^{-1} (δ-lactone), IR superposable with an authentic sample; UV : 255, 305 nm (log ϵ 2·80, 3·06).

3.2g. (±)-6-*Methoxy mellein (XII)* : XI (60 mg) was demethylated as in the case of (IX), white needles from ether-hexane (30 mg), m.p. 93° (lit. m.p. 95–97°; Slates *et al* 1967) (Found : C, 63·14; H, 5·35; $C_{11}H_{12}O_4$ requires C, 63·46 ; H. 5·76%); IR : 1660 cm^{-1} (δ-lactone-H-bonded); UV : 252, 310 nm (log ϵ 2·89, 3·09).

3.3. *Synthesis of* 3-*Methyl*-6-7-*dimethoxy*-3,4-*dihydroisocoumarin (XXI)*:

3.3a. 2-*Nitro*-1-(3,4-*dimethoxyphenyl*)-1-*propene (XVII)*: Vetraldehyde (15 g), nitroethane (8 ml) and 20 drops of 75% ethylamine were mixed and kept in refrigerator for 8 days, during which the oily product was solidified. Recrystallised from rectified spirit. m.p. 73° (lit. m.p. 73°, Pepper and Shah 1964) (12 g).

3.3b. 1-(3,4-*Dimethoxyphenyl*)-2-*propanone (XVIII)*. XVII (20 g) was dissolved in hot water (700 ml) and ethanol (300 ml), iron powder (40 g), ferric chloride (1·6 g) and concentrated HCl (10N, 24 ml) were added to it very slowly with constant heating and stirring. The mixture was refluxed with continuous stirring for 6 to 8 hr and concentrated to half the volume. The precipitated black iron oxide was filtered out and washed with hot water and benzene. The combined washings were extracted with benzene and dried (Na_2SO_4), XVIII was obtained as brown oil after distilling benzene, and purified by distillation (10 g), B.P. 198°/20 mm (lit. 122°/0·6 mm, Pepper and Shah 1964); IR : 1710 cm^{-1} (carbonyl).

3.3c. *β-oxy-α-(3,4-dimethoxyphenyl) propane (XIX)*: $NaBH_4$ (10 g) was added slowly with stirring to a solution of XVIII (10 g) in methanol (100 ml). The mixture was stirred for 16 hr, water was added and the solution extracted with CH_2Cl_2. After drying (Na_2SO_4) it was distilled to give (XIX) as brown oil which was purified by chromatography over silica gel, using benzene as eluent (7·5 g); IR : 3400–3500 cm^{-1} (hydroxyl), 1260 cm^{-1} (secondary C–O stretching). It was used as such in the next reaction.

3.3d. 3-*Methyl*-6,7-*dimethoxyisochroman (XX)*. XIX (5 g) in dry ether (180 ml) was treated with 37% formalin solution (2 ml) and concentrated HCl (10N, 2 ml), with constant shaking. The reaction mixture was allowed to stand at room temperature for 2 hr and then warmed on a water bath at 40° for 15 min. On cooling it was diluted with water and extracted with ether. The ether extract after drying (Na_2SO_4) was evaporated to give (XX) as a white solid which was

crystallised from ethylacetate-hexane (3·0 g) m.p. 79° (Found : C, 69·10; H, 7·55; $C_{12}H_{16}O_3$ requires C, 69·23; H, 7·69%); IR : 1240 cm^{-1} (cyclic ether); NMR : δ 1·3 (3H, d, J = 6·0 Hz, $-CH_2-\underset{\underset{O}{|}}{CH}-CH_3$), 2·5 (2H, d, J = 7·0 Hz, benzylic $-CH_2-$), 3·7 (7H, complex, two $-OCH_3$ groups and $-CH_2-\underset{\underset{O}{|}}{CH}-CH_2$ signals merged), 4·6 (2H, S, $Ar-CH_2-O-$), 6·35 and 6·43 (2H, two singlets H_7 and H_8).

3.3c. *3-Methyl-6,7-dimethoxy-3,4-dihydroisocoumarin (XXI)*: (XX) (3·0 g) was treated with a solution of CrO_3 (3·5 g) in acetic acid (30 ml). The reaction mixture was kept at room temperature for 3 hr and warmed on water bath at 60° for 15 min. The mixture was cooled, diluted with water and extracted with CH_2Cl_2. The extract was washed with $NaHCO_3$, water and dried (Na_2SO_4). Evaporation of the solvent gave (XXI) as white solid, crystallised from ethylacetate-hexane (1 g), m.p. 107° (lit. m.p. 104–5°, Tirodkar and Usgaonkar 1971) (Found : C, 64·64; H, 6·60; $C_{12}H_{14}O_4$ requires C, 64·86; H 6·30%); IR : 1700 cm^{-1} (δ-lactone), 2960 cm^{-1} (CH_3 stretching), 1360 cm^{-1} (CH_3 bending), 880 cm^{-1} (single aromatic hydrogen); UV : 262, 300, 338 nm (log ϵ, 4·25, 4·0, 3·17); NMR : δ 1·4 (3H, d, J = 7·0 Hz, $-CH_2-\underset{\underset{O}{|}}{CH}-CH_3$); 2·8 (2H, d, J = 7·0 Hz, benzylic $-CH_2-$), 3·8 and 3·85 (6H, two singlets, two $-OCH_3$ groups) 4·5 (1H, m, $Ar-CH_2-\underset{\underset{O}{|}}{CH}-CH_3$), 6·6 (1H, S, H_5), 7·4 (1H, S, H_8).

3.4. *Dehydrogenation of dihydroisocoumarins*

The dimethoxy 3,4-dihydroisocoumarins (500 mg) were brominated with N-bromosuccinimide and dehydrobrominated with NEt_3 according to an earlier procedure (Narasimhan 1971) to give following isocoumarins.

3.4a. *3-Methyl-5,6-dimethoxyisocoumarin (XII)* : White needles, crystallised from ethylacetate-hexane, (200 mg), m.p. 140–1° (Found : C, 65·68; H, 5·05; $C_{12}H_{12}O_4$ requires C, 65·46; H, 5·45%); IR : 1720 cm^{-1} (δ lactone), 2900 cm^{-1} (CH_3 stretching), 825 cm^{-1} (two adjacent aromatic hydrogen); UV : 238, 248, 275, 322 nm (log ϵ 4·98, 5·03, 4·23, 3·81).

3.4b. *3-Methyl-7,8-dimethoxyisocoumarin (XIV)* : White needles, crystallised from ether-hexane (125 mg) m.p. 86–7° (Found : C, 65·18; H, 5·62; $C_{12}H_{12}O_4$ requires C, 65·46; H, 5·45%); IR : 1720 cm^{-1} (δ lactone) 2940 cm^{-1} (CH_3 stretching) UV : 235, 272, 311 nm (log ϵ 4·82, 4·11, 3·82).

3.4c. *3-Methyl-5,7-dimethoxyisocoumarin (XV)* : White solid, crystallised from ether-hexane (200 mg), m.p. 147° (Found : C, 65·60; H, 5·35; $C_{12}H_{12}O_4$ requires C, 65·46; H, 5·45%); IR : 1720 cm^{-1} (δ-lactone), 2960 cm^{-1} (CH_3 stretching), 880 cm^{-1} (one aromatic hydrogen); UV : 251, 285, 320 nm (log ϵ 2·97, 30·7, 3·1).

3.4d. 3-*Methyl*-5,8-*dimethoxyisocoumarin* (*XVI*): Slightly yellowish needles, crystallised from ether-hexane (150 mg), m.p. 123° (Found : C, 65·69; H, 5·39; $C_{12}H_{12}O_4$ requires C, 65·46; H, 5·45%); IR : 1730 cm^{-1} (δ lactone), 2910 cm^{-1} (CH_3 stretching); UV : 252, 291, 330 nm (log ϵ 2·92, 3·07, 3·1).

3.4e. 3-*Methyl*-6,7-*dimethoxyisocoumarin* (*XXII*) : Slightly yellowish compound, crystallised from etherhexane (300 mg) m.p. 129–30° (lit. m.p. 130–31°, Tirodkar and Usgaonkar 1971); (Found : C, 65·86; H, 5·33; $C_{12}H_{12}O_4$ requires C, 65·46; H, 5·45%); IR : 1720 cm^{-1} (δ lactone), 2900 cm^{-1} (CH_3 stretching), 880 cm^{-1} (single aromatic hydrogen); UV : 325 nm (log ϵ 3·86).

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References

Ballio A, Barchellona S and Santurbano B 1966 *Tetrahedron Lett.* **31** 3723
Banerjee P K and Chaudhury D N 1964 *J. Indian Chem. Soc.* **B41** 221
Bhide B H and Gupta V P 1977 *Indian J. Chem.* **B15** 512
Bhide B H and Shah K K 1980 *Indian J. Chem.* **B19** 9
Bose N K and Chaudhury D N 1964 *Tetrahedron* **20** 49
Bose N K and Chaudhury D N 1969 *J. Indian Chem. Soc.* **46** 15
Govindachari T R, Patankar S J and Viswanathan N 1971 *Phytochemistry* **10** 1603
Logan W R and Newbold G T 1957 *Chem. and Ind. (London)*, p. 1485
Mitscher L A, Andres W W and MacCrae W 1964 *Experientia* **20** 258
Narasimhan N S and Bhide B H 1971 *Tetrahedron* **27** 6171
Nishikawa H 1933 *J. Agri. Chem. Soc. Jpn.* **9** 771
Pepper J M and Shah M 1964 *Can. J. Chem.* **42** 113
Slates H L, Webber S and Wendlar N L 1967 *Separatum of Chima.* **21** 468
Sondheimer E 1957 *J. Am. Chem. Soc.* **79** 5036
Tirodkar R B and Usgaonkar R N 1971 *J. Indian Chem. Soc.* **48** 192