

SYNTHETIC STUDIES ON MEDIUM AND LARGE RING ESTERS

N. N. KULKARNI, V. S. KULKARNI, S. R. LELE and B. D. HOSANGADI*

Department of Chemistry, University of Bombay,
 Vidyanagari, Bombay 400 098,
 India.

(Received in UK 11 May 1988)

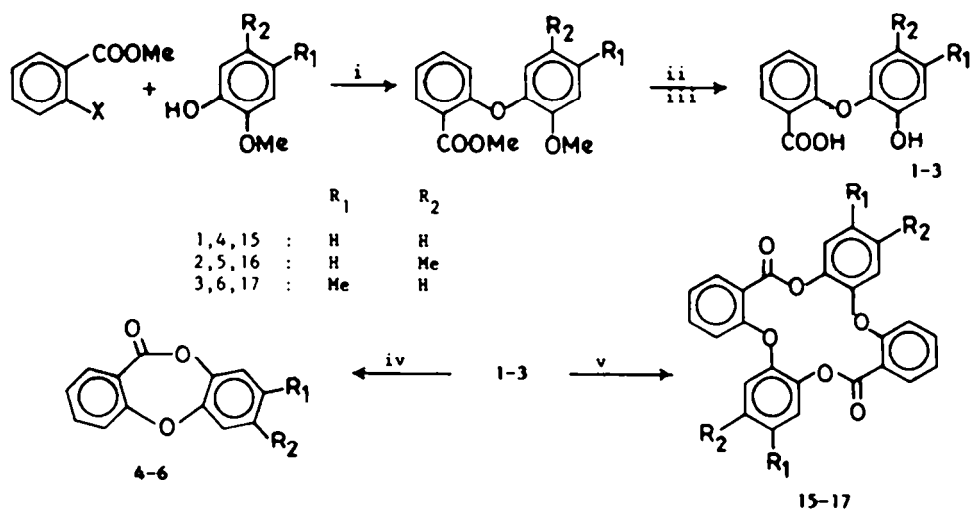
Abstract - The syntheses of 7, 14 and 20 membered heterocyclic esters have been reported in connection with the study of photobehaviour of such type of compounds.

In recent years conformational flexibility and the influence it can have on photoreactions of certain classes of compounds has aroused considerable interest.¹ Effect of ring size on photo-reactivity as such has not been analysed. Cyclic esters afford examples of substrates wherein variation in number of photosensitive -CO-O- chromophore leads to compounds of varying sizes expectedly with different conformational flexibility.

The above investigation interalia necessitated synthesis of cyclic esters of different ring sizes which had to precede photochemical studies. In this paper we describe the synthesis of model 7, 14 and 20 membered cyclic esters, the synthesis of 8, 12, 16 membered cyclic esters being already available.^{2,3} The studies on photoextrusion are dealt with in the separate communication.⁴

The synthesis of seven membered cyclic esters viz. 11H-dibenzo[b,e][1,4]dioxepin-11-ones (depsidones) (4-6) was accomplished^{5,6} by simple dehydration of 2-(2-hydroxyaryloxy)benzoic acids (1-3) with acetic anhydride (Scheme 1). The methoxy analogs 11 and 12 were prepared

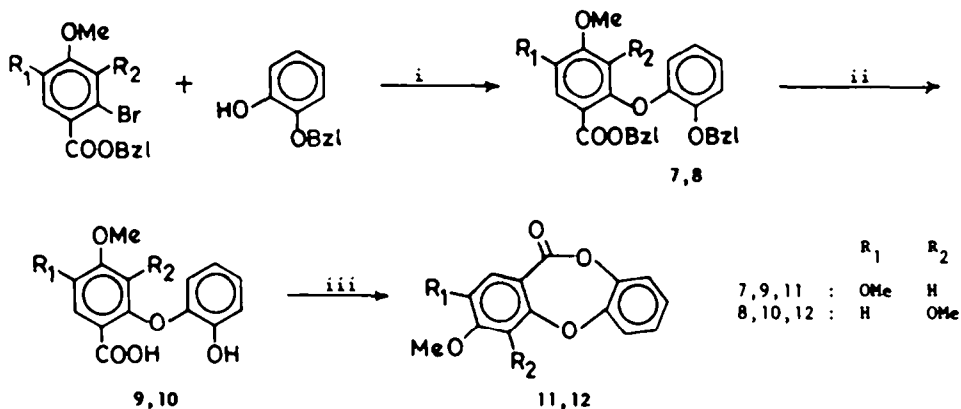
Scheme - 1



i) CuO, K₂CO₃, pyridine, ii) hydrolysis, iii) demethylation, iv) Ac₂O, v) PPE, CHCl₃

similarly from the corresponding acid substrates (9 and 10) which in turn were also synthesized as shown in Scheme 2. The mode of cyclization was found to be different when PPE (polyphosphate ester) was employed, as the same acids (1-3) yielded corresponding fourteen membered cyclic esters viz. 11H,22H-tetrabenzo[b,e,i,l][1,4,8,11] tetraoxacyclotetradecin-11,22-diones (15-17) (Scheme 1) along with the depsidones.

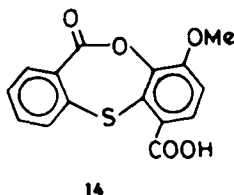
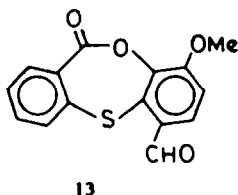
Scheme - 2



i) CuO, K₂CO₃, pyridine, ii) H₂, Pd-C, iii) Ac₂O

With a view to study the effect of functional groups on the photodecarboxylation of depsidones two model compounds 13 and 14 containing formyl and carboxylic functional groups were also synthesized.⁷

Similar dehydration of 2-(2-mercaptoaryloxy)benzoic acids (19,20) with acetic anhydride yielded seven membered 11H-dibenzo[b,e][1,4]oxathiepen-11-ones (thiadepsidones) (21, 22), whereas treatment with PPE yielded a mixture of thiadepsidones as well as corresponding fourteen membered cyclic esters, 11H,22H-tetrabenzo[b,e,i,l][1,8,4,11]dioxadithiacyclotetradecin-11,22-diones (23, 24) (Scheme 3); which were separated by column chromatography. All these compounds were characterized by elemental analysis and spectral data.



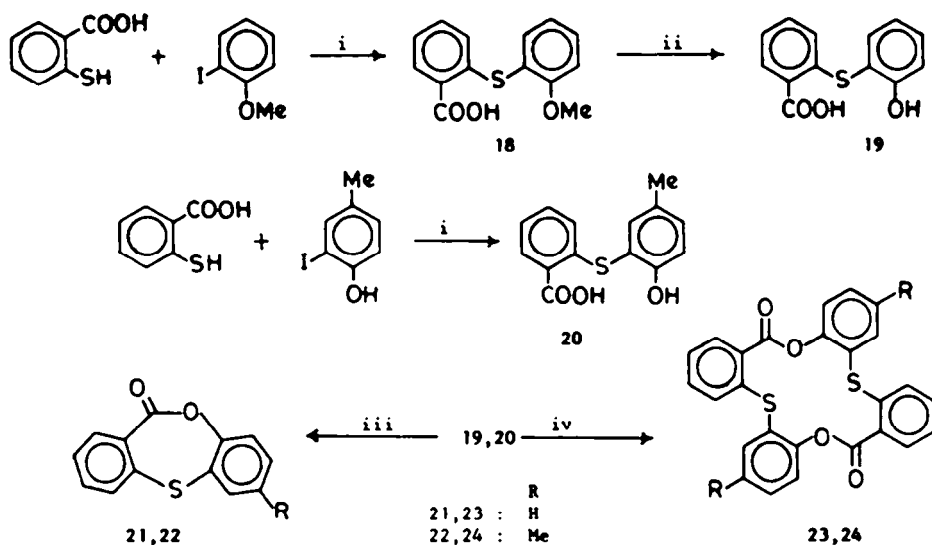
Though tetraalicylide possesses four ester linkages, alternate structures (phenyl ester type) can be envisaged, which would also possess four ester linkages. Synthesis of one such large ring compound necessary for photochemical studies was carried out. The intermolecular cyclocondensation involving two molecules each of terephthaloyl chloride and catechol was found to yield a twenty membered cyclic ester viz. 7,10:19,22-dietheno-6H,11H,18H,23H-dibenzo[b,l]-[1,4,11,14]-tetraoxacycloeicosine-6,11,18,23-tetrone (25). The MS data of this tetra-ester showed an entirely characteristic fragmentation pattern (Figure 1). The metastable transition observed at m/z 247 clearly indicated the relationship between the ion at m/z 344 and the parent ion M^+ 480 m/z .

With the cyclic esters of different sizes in hand, the study was now focussed on their photochemical behaviour which is discussed in the accompanying communication.

EXPERIMENTAL

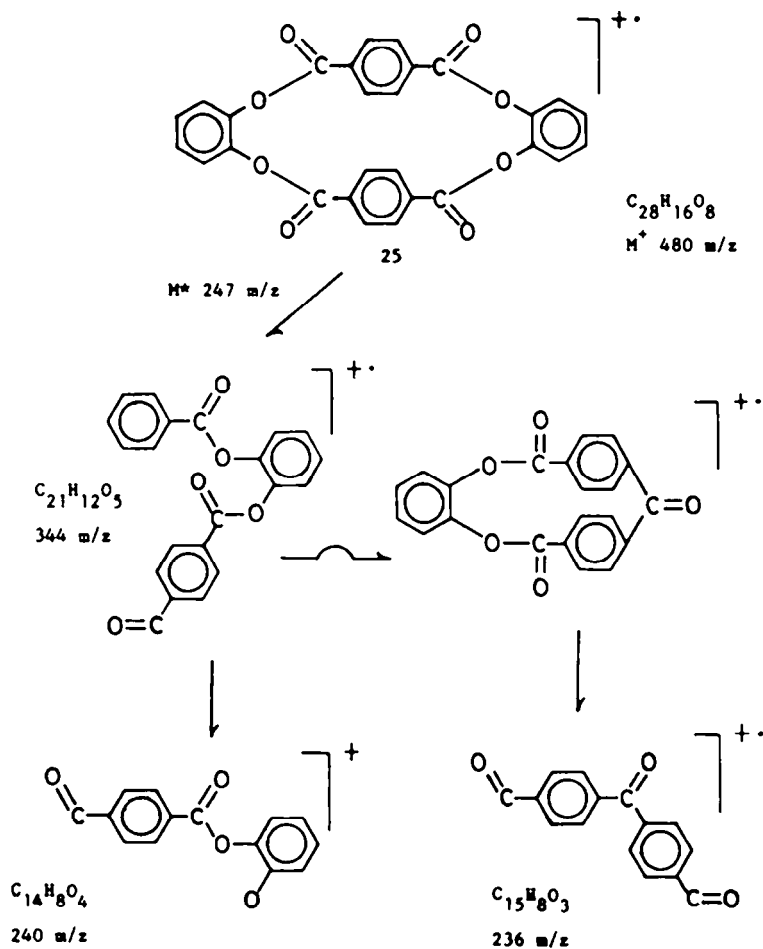
The melting points were determined in open capillaries and were uncorrected. IR spectra were recorded on a Hilger and Watts Infracord Model H-900 and Beckman Spectrophotometer Model IR-4250. Mass spectra were taken on Varian Mat CH-7 and Varian Mat CH-6 Spectrometers. PMR spectra were scanned in CDCl₃ on Varian EM-360 -60-MHz and Bruker WP-80 Spectrometers.

Scheme - 3



i) K_2CO_3 , copper acetate, ii) HBr, AcOH, iii) Ac_2O iv) PPE, $CHCl_3$

Figure - 1



UV spectra were recorded in spectral grade methanol on Bausch and Lomb Spectronic 2000.

2,3-Dimethoxy-11H-dibenzo[b,e][1,4]-dioxepin-11-one (11).— 2-Bromo-4,5-dimethoxybenzoic acid⁸ (7.88 g, 30 μ mol) and 4.5 ml of benzyl chloride were taken in 30 ml of dry DMF and anhydrous K_2CO_3 (3 g) was added to it. The reaction mixture was heated on water bath. After 6 h the reaction was decomposed over crushed ice with vigorous stirring. The crude oil obtained was extracted with ethyl acetate. Combined ethyl acetate extract was washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated. The semisolid obtained was vacuum distilled (2 mm) to furnish a colourless compound, benzyl 2-bromo-4,5-dimethoxybenzoate, m.p. 67°. Yield: 8.95 g (85%).

This ester (7.0 g, 20 μ mol) and catechol monobenzyl ether (3.72 g, 20 μ mol) were taken in a three-neck round bottom flask. Dry pyridine (35 ml) and anhydrous K_2CO_3 (5 g) were added to it. Dry nitrogen gas was passed through the reaction mixture. The stirred reaction mixture was heated to 130° (oil bath) and CuO (0.150 g) was added to the mixture. The temperature was maintained at 130° for two hours and then it was raised to 150°. The stirred reaction mixture, under dry nitrogen was refluxed at this temperature for 14 hours. The reaction mixture was cooled to room temperature and then it was decomposed over crushed ice and acidified with 2N HCl. The solution was extracted with chloroform. The combined chloroform extract was washed with 2N HCl followed by brine solution. The dried (Na_2SO_4) chloroform extract was concentrated to yield a viscous oil; which was chromatographed over silica-gel column. The petroleum-ether (60 - 80°) - ethyl acetate (95 : 5) fraction yielded the corresponding diaryl ether (7), m.p. 87-89°. Yield : 5.93 g (63.1%).

Compound 7 (2.0 g, 4.2 μ mol) and Pd/C (10% palladium on carbon; 0.2 g) were taken in ethyl acetate (40 ml). It was shaken over hydrogen at 60 psi. The reaction was monitored on tlc ($CHCl_3$) after every hour. The reaction was complete after three hours. The reaction mixture was filtered to remove the reagent and the filtrate was charcoalised and concentrated to yield the required hydroxy-acid (9), m.p. 215-16°. Yield : 0.5 g (40.5%).

A mixture of the acid (9) (0.29 g, 1 μ mol) and acetic anhydride (15 ml) was refluxed for five hours at 145° in an oil bath. The excess acetic anhydride was distilled out under vacuum. The residue was poured on crushed ice. The viscous oil was then extracted with ether. The combined ether extracts were washed successively with 2% Na_2CO_3 solution and water. The extract was dried (Na_2SO_4) and concentrated to afford an oil. Crystallisation of this oil from benzene-petroleum ether yielded the corresponding depsidone (11). m.p. 121-22°. Yield : 0.16 g (58%). (Found: C, 65.94%; H, 4.42%; $C_{15}H_{12}O_5$ requires: C, 66.17%; H, 4.44%); λ_{max} : 265, 306 nm, IR (KBr): 2940, 2920, 1720 (lactone) cm^{-1} ; PMR ($CDCl_3$) δ 3.89 (s, 3H, -OCH₃), 3.96 (s, 3H, -OCH₃), 6.78 (1H, H at C-4), 7.25-7.3 (m, 4H, aromatic), 7.41 (1H, H at C-1).

3,4-Dimethoxy-11H-dibenzo[b,e][1,4]-dioxepin-11-one (12).— 30 μ mol (7.83 g) of 2-bromo-3,4-dimethoxybenzoic acid⁹ were benzylated with 4.2 ml of benzyl chloride using the same procedure mentioned above to obtain benzyl 2-bromo-3,4-dimethoxybenzoate, m.p. 64-65° (benzene-petroleum ether). Yield : 8.4 g (80%).

This ester (21 g, 60 μ mol) and catechol monobenzyl ether (12 g, 60 μ mol) were reacted in pyridine and K_2CO_3 as mentioned in the case of compound 7 to yield the corresponding diaryl ether (8). m.p. 87-88°. Yield : 24.1 g (67%).

Debenzylation of this diaryl ether (2 g, 4.2 μ mol) using 10% Pd/C (0.2 g) in 40 ml ethyl acetate resulted in yielding the hydroxy-acid (10), m.p. 165°. Yield : 0.5 g (40.5%).

Dehydration of the hydroxy-acid (10) (1.45 g, 5 μ mol) using 20 ml of acetic anhydride and work-out of the reaction mixture in a manner similar to that described for compound 11 yielded the required depsidone (12). m.p. 116°. Yield : 0.843 g (62%). (Found: C, 65.96%; H, 4.15%; $C_{15}H_{12}O_5$ requires: C, 66.17%; H, 4.44%). λ_{max} (MeOH): 268 nm. IR (KBr): 2960, 2900, 1730 cm^{-1} (lactone). PMR ($CDCl_3$): δ 3.94 (s, 3H, -OCH₃), 4.07 (s, 3H, -OCH₃), 7.01-7.43 (m, 5H, aromatic), 7.76 (1H, H at C-1).

11H-Dibenz[b,e][1,4]-oxathiepin-11-one (21).— A mixture of n-amyl alcohol (17 ml), thiosalicylic acid (4.9 g, 30 μ mol), 2-iodoanisole (7.5 g, 30 μ mol), anhydrous K_2CO_3 (4.6 g) and copper acetate (0.1 g) was refluxed for 16 h. Aqueous sodium hydroxide (25%, 25 ml) was added and amyl alcohol was removed by steam distillation. The alkaline aqueous layer was acidified with HCl to obtain 2-(2-methoxyphenylthio)benzoic acid (18) which was crystallised from ethanol as colourless needles, m.p. 203°. Yield : 8 g (96.3%).

A mixture of the acid (18) (5 g, 10 μ mol), hydrobromic acid (60%) (25 ml) and acetic acid (10 ml) was refluxed for 2 h at 135-140° in an oil bath. The reaction mixture was decomposed in ice water. The product was extracted in ether. The ethereal layer was washed with sodium bicarbonate. The bicarbonate extract was acidified to get a crude product which was crystallized from benzene to yield colourless plates of the hydroxy-acid (19), m.p. 175°. Yield : 2 g (42%).

8 μ moles (2 g) of this compound were dissolved in acetic anhydride and refluxed at 145-148° for 8 h. The excess acetic anhydride was distilled off and the reaction mixture was decomposed in ice and water. Extraction with ether yielded the depsidone (21) which was re-crystallized from benzene; colourless needles, m.p. 124°. Yield : 1 g (54%). (Found: C, 68.72%; H, 3.97%; S, 14.13%; $C_{13}H_8O_2S$ requires: C, 68.42%; H, 3.50%; S, 14.03%). λ_{max} (MeOH) : 251 nm, IR (KBr) : 1740 (lactone) and 1590 cm^{-1} .

7-Methyl-11H-dibenz[b,e][1,4]-oxathiepin-11-one (22).— A mixture of 2-iodo-4-methylphenol¹⁰ (7 g, 20 μ mol), n-amyl alcohol (25 ml), thiosalicylic acid (5 g, 30 μ mol), anhydrous K_2CO_3 (5 g) and copper acetate (0.1 g) was refluxed for 16 h. Aqueous sodium hydroxide (25%, 25 ml) was added and amyl alcohol was removed by steam distillation. The alkaline aqueous layer was made acidic with HCl to give 2-(2-hydroxy-5-methylphenylthio)benzoic acid (20), crystallised

from ethanol as colorless plates, m.p. 251°. Yield : 7 g (87%). (Found : C, 64.23; H, 4.81%; S, 12.41%; $C_{14}H_{12}O_3S$ requires : C, 64.61%; H, 4.61%; S, 12.31%). IR (KBr) : 3400 (-OH), 1690 (C = O) cm^{-1} .

This acid (5 g, 19 μ mol) was dissolved in acetic anhydride and refluxed at 145-148° for 8 hr. The excess acetic anhydride was distilled off and the reaction was decomposed in ice and water. The product was extracted with ether, washed with sodium bicarbonate (4 x 25 ml) and then with water (50 ml). Removal of ether afforded compound 22 which was crystallized from benzene, colorless needles, m.p. 107°. Yield : 3 g (64.5%). (Found : C, 69.64%; H, 3.79%; S, 13.52%; $C_{14}H_{10}O_2S$ requires : C, 69.42%; H, 4.13%; S, 13.22%). λ_{max} (methanol) : 251, 305 nm. IR (KBr) : 1730 cm^{-1} (lactone); PMR (CDCl₃) : δ 2.34 (s, 3H, CH₃), 7.06-7.88 (7H, m, aromatic protons).

General procedure for the preparation of cyclic esters (15-17, 23 and 24).— A mixture of 5 μ mol of the appropriate acid (1-3, 19 and 20), 5 μ mol of polyphosphate ester and 30 ml chloroform was heated to reflux for one hour. The reaction mixture was cooled and the chloroform layer was washed with water and 5% sodium bicarbonate solution. The dried (Na₂SO₄) chloroform extract was concentrated and subjected to chromatography on silica-gel column. The corresponding seven membered cyclic esters (depsidones) (45, 17%; 56, 18%; 66, 19%; 21, 44.4% and 22, 49%) which eluted first were identified by comparison with authentic samples. Continuation of eluting the column with more polar solvents afforded the corresponding fourteen membered cyclic esters 15-17, 23 and 24.

11H,22H-tetrabenzo[b,e,i,l][1,4,8,11]tetraoxacyclotetradecin-11,22-dione (15)¹¹— m.p. 202° Yield : 48%. Found : C, 73.62%; H, 3.47%. $C_{26}H_{16}O_6$ requires : C, 73.58%; H, 3.80%. λ_{max} (MeOH) : 289 nm. IR (KBr) : 1765 cm^{-1} , PMR (CDCl₃) : δ 6.88 to 7.78 (aromatic protons), MS : m/z 424 (M⁺).

8,19-Dimethyl-11H,22H-tetrabenzo[b,e,i,l][1,4,8,11]tetraoxacyclotetradecin-11,22-dione (16)¹¹— m.p. 272°. Yield : 46.9%. Found C, 74.2%; H, 4.5%. $C_{28}H_{20}O_6$ requires : C, 74.43%; H, 4.42%. λ_{max} (MeOH) : 292 nm. IR (KBr) : 1755 cm^{-1} , PMR (CDCl₃) : δ 2.42 (s, 6H, CH₃), 6.82-7.7 (m, 14H, aromatic protons), MS : m/z 452 (M⁺).

7,18-Dimethyl-11H,22H-tetrabenzo[b,e,i,l][1,4,8,11]tetraoxacyclotetradecin-11,22-dione (17)— m.p. 256°. Yield : 47%. Found : C, 74.3%; H, 4.15%. $C_{28}H_{20}O_6$ requires : C, 74.33%; H, 4.46%. λ_{max} (MeOH) : 291 nm; IR (KBr) : 1760 cm^{-1} , PMR (CDCl₃) : δ 2.4 (s, 6H, CH₃), 6.88-7.72 (m, 14H, aromatic protons).

11H,22H-tetrabenzo[b,e,i,l][1,8,4,11]dioxadithiacyclotetradecin-11,22-dione (23)— m.p. 229°. Yield : 12.2%. Found : C, 68.64%; H, 3.70%; S, 14.32%. $C_{26}H_{16}O_4S_2$ requires : C, 68.42%; H, 3.5%; S, 14.03%. λ_{max} (MeOH) : 253, 283 nm. IR (KBr) : 1730 cm^{-1} , MS : m/z 456 (M⁺), 228.

7,18-Dimethyl-11H,22H-tetrabenzo[b,e,i,l][1,8,4,11]dioxadithiacyclotetradecin-11,22-dione (24)— m.p. 109°. Yield : 20.3%. Found : C, 69.34%; H, 4.08%; S, 13.24%. $C_{28}H_{20}O_4S_2$ requires : C, 69.42%; H, 4.13%; S, 13.22%. λ_{max} (MeOH) : 289 nm. IR (KBr) : 1730 cm^{-1} , PMR (CDCl₃) : δ 2.33 (s, 6H, CH₃), 7.1-7.56 (m, 14H, aromatic protons).

7,10:19,22-Dietheno-6H,11H,18H,23H-dibenzo[b,l][1,4,11,14]tetraoxacycloicosine-6,11,18,23-tetrone (25). Terephthaloyl chloride (1.7 g, 8.4 μ mol) was added to a mixture of catechol (0.9 g, 8.4 μ mol) in pyridine (5.0 ml). The reaction mixture was allowed to stand overnight and then decomposed in ice-cold water. The solid formed was thoroughly washed with saturated sodium bicarbonate solution followed by water to remove unreacted starting components. The residue left behind was crystallized from excess volume of benzene to obtain the required tetrone; m.p. 220°. Yield : 1.4 g (70%). Found : C, 70.21%; H, 3.05%. $C_{28}H_{16}O_8$ requires : C, 70.00%; H, 3.33%; IR (KBr) 1720 cm^{-1} , MS : m/z 480 (M⁺), 247 (M⁺) (Figure 1).

Acknowledgement— One of the authors (VSK) thanks University Grants Commission for financial assistance.

REFERENCES

1. P. J. Wagner : Acc. Chem. Res., 16, 461 (1983).
2. V. D. Gaitonde and B. D. Hosangadi : Indian J. Chem., 14B, 97 (1976).
3. C. M. Farias and B. D. Hosangadi : Indian J. Chem., 15B, 997 (1977).
4. V. S. Kulkarni, N. N. Kulkarni, S.R. Lele and B. D. Hosangadi : Tetrahedron, following communication.
5. D. S. Noyce and J. W. Weldon : J. Am. Chem. Soc., 74, 401 (1952).
6. F. Fujikawa, K. Hirai, N. Ishikawa and A. Maki : Yakugaku Zasshi, 63, 1172 (1963).
7. N. N. Kulkarni and B. D. Hosangadi : Unpublished results.
8. R. Paschorr : Ann., 33, 391 (1912).
9. T. A. Henry and T. M. Sharp : J. Chem. Soc., 2285 (1930).
10. C. M. Suter and R. D. Schuetz : J. Org. Chem., 16, 1117 (1951).
11. S. R. Lele and B. D. Hosangadi : Indian J. Chem., 18B, 533 (1979).