Pak. j. sci. ind. res., vol.40, nos 5-12, May-December 1997

# SYNTHESIS OF HETERO-BICYCLIC COMPOUNDS
## *Part-IX.* Formation of 2,2-disubstituted 4,5-dioxo-pyridino [4,3-d] [1,3]dioxins

M.A. Butt*, R. Kemal, A. Salam and A. Akhtar

*PCSIR Laboratories Complex, Off University Road, Karachi-75280, Pakistan*

(Received January 26, 1994; revised April 16, 1997)

Chloropyranodioxins (I) prepared by the reaction of malonyl chloride with mixed ketone were converted into 7-(phenylamino)-pyranodioxins (II) which underwent the phenoxide rearrangement to yield the corresponding pyridinodioxins (III), whose structures were determined by chemical conversions and spectroscopic studies.

***Key words:*** Chloropyranodioxin, Pyridinodioxin, Hetero-bicyclic compounds.

### Introduction

Several methods for the synthesis of substituted pyridines have been reported in literature [1-10]. The authors have demonstrated synthetic utility of chloropyranodioxin (I) in their preceding papers of the series [11,12].

In continuation of the previous work [12], preparation of 2, 2-disubstituted-4, 5-dioxo-7-(phenylamino)-pyranodioxins (II) from chloro compounds (I) and their subsequent rearrangement to the corresponding 2,2-disubstituted-4, 5-dioxo-pyridinodioxins (III) under the influence of sodium phenoxide in phenol have been investigated. The characterization of these compounds is accomplished by spectroscopic studies supported by elemental analysis and formation of derivatives.

### Experimental

Melting points were determined with a Thomas-Hoover Capillary apparatus and are uncorrected. UV and IR spectra were recorded on Beckman 36 and Perkin Elmer 283 spectrophotometer respectively.

*7-Chloro-2-ethyl-2-methyl-4, 5-dioxopyrano [4,3-d] [1,3]dioxin (I,R'=$CH_3$-, R"=$C_2H_5$):-* A mixture of malonyl chloride (9.7ml, 0.1 mole) and methyl ethyl ketone (4.5 ml, 0.05 mole) was heated on a water bath until a solid product appeared. Trituration of the product with ether gave 7-chloro-2-ethyl-2-methyl-4,5-dioxopyrano[4,3-d] [1,3] dioxin (8.5g, 70%) (I,R' = $CH_3$, R" = $C_2H_5$) which was crystallized from benzene (m.p. 160°C). Found: C,49.4; H,3.5. $C_{10}H_9O_5Cl$ requires C, 49.1; H, 3.7%.

Other chloropyranodioxins prepared similarly are listed in Table 1.

*2-Ethyl-2-methyl-4,5-dioxo-7-(phenylamino)-pyrano [4,3-d] [1,3] dioxin (R'=$CH_3$, R"=$C_2H_5$):-* To a solution of 7-chloro-2-ethyl-2-methyl-4, 5-dioxo-pyrano [4,3-d] [1,3] dioxin (4.9g, 0.02 moles) (I,R'=$CH_3$,R"=$C_2H_5$) in $CHCl_3$ (10 ml) aniline (3.7g; 0.04 mole) in $CHCl_3$ (10ml) was added with constant stirring. A solid product was obtained which was washed with water and dried. 2-Ethyl-2-methyl-4, 5-dioxo-7- (phenylamino)-pyrano [4,3-d] [1,3] dioxin (4.9g, 82%) (II, R'=$CH_3$, R"=$C_2H_5$) was crystallized from a mixture of $CHCl_3$ and $CH_3OH$ (m.p. 163°C). Found: C, 63.8; H, 4.9; N, 4.5. $C_{16}H_{15}NO_5$ requires C, 63.8; H,4.9; N, 4.6%.

Other 2,2-disubstituted -4,5-dioxo-7-(phenylamino)-pyrano [4,3-d] [1,3] dioxins (II) were prepared as above and are listed in Table 2.

*2-Ethyl-2-methyl-4, 5-dioxo-7-hydroxy-6-phenyl-pyridino [4,3-d] [1,3] dioxin (III, R'=$CH_3$, R"=$C_2H_5$):-* 2-Ethyl-2-methyl-4,5-dioxo-7-(phenylamino)-pyrano [4,3-d] [1,3]dioxin (II, R'=$CH_3$, R"=$C_2H_5$) (3g, 0.01 moles) was added to a solution of Na (0.92g, 4 moles) in phenol (30 ml) and the mixture was heated at 120°C for 2 minutes. The solution was cooled, diluted with water and extracted with ether to recover excess phenol. The ethereal layer was extracted with water and the combined aqueous extracts (130 ml) were acidified with HCl (3N) to yield a solid product. The product, 2-ethyl-2-methyl-4,5-dioxo-7-hydroxy-6-phenyl-pyridino [4,3-d][1,3] dioxin (III,R'=$CH_3$, R"=$C_2H_5$; 2.6g, 87%) was crystallized from MeOH, mp 210°C. It gave a reddish colouration with aq. $FeCl_3$ and showed effervescence with aq. $NaHCO_3$. Found: C, 63.8; H, 4.8; N, 4.5. $C_{16}H_{15}NO_5$ requires C, 63.8; H, 4.9; N, 4.6%.

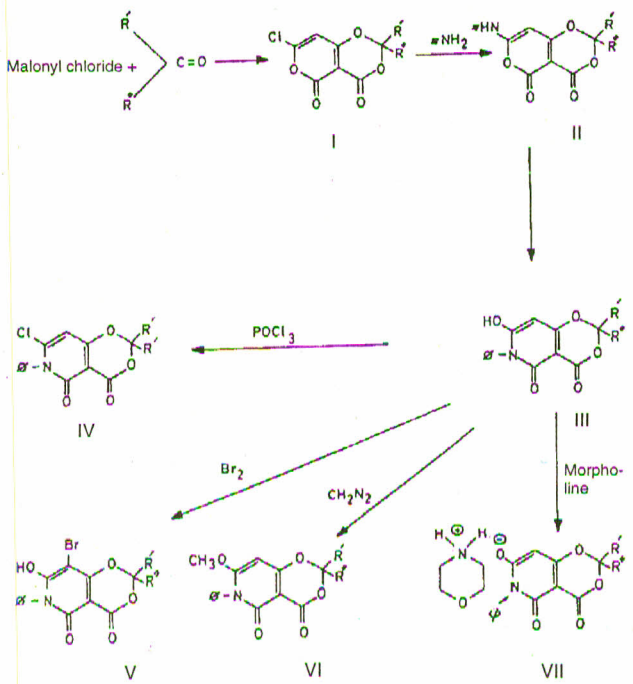
The rearrangement products III of other arylamino-2, 2-disubstituted-pyranodioxins with sodium phenoxide in phenol are listed in Table 3.

7-Chloro-2-ethyl-2-propyl-4, 5-dioxo-6-phenyl-pyridino [4,3-d] [1,3] dioxin (IV,R'=$C_2H_5$, R"=$C_3H_7$):- 2-Ethyl-7-hydroxy-4, 5-dioxo-6-phenyl-2-propyl-pyridino [4,3-d][1,3] dioxin (III, R'=$C_2H_5$, R"=$C_3H_7$; 0.5g) and $POCl_3$ (10ml) were

*PCSIR Laboratories Complex, Shahrah-e-Jalaluddin Roomi, Lahore-54600, Pakistan.

TABLE 1. FORMATION OF 2,2-DISUBSTITUTED-7-CHLORO-4,5-DIOXOPYRANO [4,3-d] [1,3] DIOXINS (I).

| No. | Keto compound | Malonyl chloride | 2.2-disubstituted-7-chloro-dioxo -pyrano [4,3-d][1,3] dioxins (I) | Yield g. | m.p. C° | Molecular Formula | Analysis Found C | Found H | Required C | Required H |
|---|---|---|---|---|---|---|---|---|---|---|
| 1. | $CH_3COC_2H_5$ (4.5ml) | 9.7 ml | 7-chloro-2-ethyl-2-methyl-4, 5-dioxopyranodioxin | 1.6 | 160 | $C_{10}H_9O_5Cl$ | 49.0 | 3.6 | 49.0 | 3.7 |
| 2. | $C_6H_5COCH_3$ (2.5g) | 4.0 ml | 7-chloro-2-mehtyl-2-phenyl-4, 5-dioxopyranodioxin | 3.0 | 147 | $C_{14}H_9O_5Cl$ | 57.5 | 3.0 | 57.4 | 3.1 |
| 3. | $C_6H_5COC_2H_5$ (5.6g) | 8.0 ml | 7-chloro-2-ethyl-2-phenyl-4, 5-dioxopyranodioxin | 10.0 | 105 | $C_{15}H_{11}O_5Cl$ | 58.8 | 3.6 | 58.7 | 3.6 |
| 4. | p-Cl-$C_6H_4COCH_3$ (6.4g) | 8.0 ml | 7-chloro-2-methyl-2-(p-chloro-phenyl)-4,5-dioxopyranodioxin | 7.0 | 129 | $C_{14}H_8O_5Cl_2$ | 51.6 | 2.2 | 51.4 | 2.4 |
| 5. | $C_6H_5CO.COC_6H_5$ (8.7g) | 8.0 ml | 7-chloro-2-pheynl-2-benzoyl-4, 5-dioxopyranodioxin | 7.8 | 88 | $C_{20}H_{11}O_6Cl$ | 62.8 | 2.7 | 62.7 | 2.8 |
| 6. | $CH_3CO(CH_2)_3CH_3$(2.6ml) | 4.0 ml | 2-butyl-7-chloro-2-methyl-4, 5-dioxopyranodioxin | 2.5 | 91 | $C_{12}H_{13}O_5Cl$ | 52.9 | 4.5 | 52.8 | 4.7 |
| 7. | $C_2H_5CO(CH_2)_2CH_3$(2.6ml) | 4.0 ml | 7-chloro-2-methyl-2-propyl-4, 5-dioxopyranodioxin | 3.1 | 110 | $C_{12}H_{13}O_5Cl$ | 52.8 | 4.6 | 52.8 | 4.7 |
| 8. | $CH_3(CH_2)_2CO(CH_2)_2CH_3$ (3.0ml) | 4.0 ml | 7-chloro-2, 2-dipropyl-4, 5-dioxopyranodioxin | 3.0 | 135 | $C_{13}H_{15}O_5Cl$ | 54.6 | 5.1 | 54.4 | 5.2 |




heated on a water bath for 30 minutes. Excess of $POCl_3$ was removed under reduced pressure and the residue was crystallized from EtOH/water (0.2g, 38.5%), m.p. 160°C. Found; C, 62.0; H, 5.1; N, 3.8. $C_{12}H_{13}O_5Cl$ requires C, 62.1; H, 5.2; N, 4.0%.

*8-Bromo-2-ethyl-7-hydroxy-4,5-dioxo-2,6-diphenyl-pyridino-[4,3-d] [1,3]dioxin (V,R'=$C_6H_5$, R"=$C_2H_5$):-* To a solution of the compound (III, R'=$C_6H_5$, R"=$C_2H_5$ 0.5g) in $CHCl_3$ (20 ml), bromine in $CHCl_3$ was added drop wise till an orange colour persisted. The reaction mixture was kept at room temperature for 1 h. and the solvent was removed under reduced pressure. A solid bromo product (V, R'=$C_6H_5$; R"=$C_2H_5$; 0.35g) was obtained and recrystallized from MeOH. m.p. 124°C. Found: C, 57.7; H, 3.5. $C_{21}H_{16}NO_5$ Br requires C, 57.0; H, 3.6; N, 3.2%.

*2-Butyl-7-methoxy-2-methyl-4, 5-dioxo-6-phenyl-pyridino [4,3-d] [1,3] dioxin (VI, R'=$CH_3$, R"=$C_4H_9$):-* To 2-butyl-7-hydroxy-2-methyl-4, 5-dioxo-6-phenyl-pyridino [4,3-d] [1,3] dioxin (III, R'=$CH_3$, R"=$C_4H_9$; 0.5g) in ether, was added a solution of diazomethane in ether until yellow color persisted. The solution was kept for 2 h. in a refrigerator and the solvent was removed. The residue yielded a product on trituration with ether. The product 2-butyl-7-methoxy-2-methyl-4, 5-dioxo-6-phenyl-pyridino [4,3-d] [1,3] dioxin (VI R'=$CH_3$, R"=$C_4H_9$; 0.23g) was crystallized from MeOH, mp 149°C. Found: C,66.5; H,5.9; N,4.0. $C_{19}H_{21}NO_5$ requires C,66.5; H,6.1; N,4.1%.

*Morpholinium salt (VII, R'=$C_2H_5$ and R"=$C_3H_7$) of 7-hydroxy product (III, R'=$C_2H_5$, R"=$C_3H_7$):-* To the compound (0.5g) (III, R'=$C_2H_5$, R"=$C_3H_7$) in $CHCl_3$ (10ml) was added morpholine (0.5 ml) and the mixture was refluxed for 3 minutes. The solvent was removed under reduced pressure and the residue obtained (0.5g, 79%) was recrystallized from MeOH, m.p. 193°C. Found C, 63.5; N, 6.7. $C_{22}H_{28}N_2O_6$ requires C, 63.4; N, 6.7%.

## Results and Discussion

We have studied the formation of some hitherto unreported chloropyranodioxins (I) by the reaction of malonyl chloride with mixed ketones. These chloropyranodioxins (I) reacted with aniline to yield 2,2-disubstituted-7-(phe-

TABLE 2. FORMATION OF 2,2-DISUBSTITUTED 4,5-DIOXO-7-(PHENYLAMINO)-PYRANO [4,3-d][1,3] DIOXINS.

| No. | 2,2-disubstitute-7-chloro-4,5-dioxo-pyranodioxin(I) R' | R" | Quantity (g) | Aniline (g) | 2,2-disubstituted-4,5-dioxo 7-(phenylamino) pyrano-[4,3-d][1,3] dioxin(II) | Yield % | m.p. C° | Molecular Formula | Analysis Found C | H | N | Required C | H | N | UV Light Absorption 95% MeOH $\lambda_{max}$(nm) | Logε |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. | $CH_3$- | $C_2H_5$- | 4.9 | 3.7 | 2-ethyl-2-methyl-4,5-dioxo 7-(phenylamino) pyranodioxin | 82 | 163 | $C_{16}H_{15}NO_5$ | 63.8 | 4.9 | 4.6 | 63.8 | 4.8 | 4.6 | 341 | 4.72 |
| 2. | $CH_3$- | $C_6H_5$- | 7.0 | 4.4 | 2-methyl-2-phenyl-4,5-dioxo -7-(phenylamino) pyranodioxin | 84 | 147 | $C_{20}H_{15}NO_5$ | 68.8 | 4.0 | 3.9 | 68.7 | 4.3 | 4.0 | 344 | 4.48 |
| 3. | $C_2H_5$- | $C_6H_5$- | 8.0 | 4.7 | 2-ethyl-2-phenyl-4,5-dioxo-7-(phenylamino)-pyranodioxin | 78 | 156 | $C_{21}H_{17}NO_5$ | 69.9 | 4.4 | 3.8 | 69.9 | 4.6 | 3.8 | 344 | 4.52 |
| 4. | $CH_3$- | p-Cl-$C_6H_4$- | 6.0 | 3.4 | 2-(p-chlorophenyl)-2-methyl -4,5-dioxo-7-(phenylamino) -pyranodioxin | 91 | 160 | $C_{20}H_{14}NO_5Cl$ | 62.4 | 3.3 | 3.4 | 62.5 | 3.6 | 3.6 | 345 | 4.83 |
| 5. | $C_6H_5$- | $C_6H_5CO$- | 6.0 | 2.9 | 2-benzoyl-4,5-dioxo-phenyl-7-(phenylamino)-pyranodioxin | 41 | 180 | $C_{26}H_{17}NO_6$ | 71.0 | 3.7 | 3.2 | 71.1 | 3.9 | 3.2 | 351 | 4.29 |
| 6. | $CH_3$- | n-$C_4H_9$- | 6.5 | 3.7 | 2-butyl-2-methyl-4,5-dioxo-7-(phenylamino)-pyranodioxin | 73 | 161 | $C_{18}H_{19}NO_5$ | 65.8 | 5.6 | 4.2 | 65.6 | 5.7 | 4.2 | 343 | 4.55 |
| 7. | $C_2H_5$- | n-$C_3H_7$- | 6.5 | 3.7 | 2-ethyl-4,5-dioxo-7-(phenyl-amino)-2-propyl-pyranodioxin | 77 | 154 | $C_{18}H_{18}NO_5$ | 65.2 | 5.5 | 4.0 | 65.6 | 5.7 | 4.2 | 343 | 4.18 |
| 8. | n-$C_3H_7$- | n-$C_3H_7$- | 7.0 | 3.7 | 4,5-dioxo-7-(phenylamino)-2,2-dipropyl-pyranodioxin | 62 | 172 | $C_{19}H_{21}NO_5$ | 66.0 | 6.1 | 4.0 | 66.4 | 6.1 | 4.1 | 342 | 4.66 |

TABLE 3. FORMATION OF 2,2-DISUBSTITUTED-7-HYDROXY-4,5-DIOXO-6-PHENYL-PYRIDINO [4,3-d] [1,3] DIOXINS.

| No. | 7-(Phenylamino)-pyrano dioxin (II) R' | R" | Quantity (g) | Sodium/ Phenol | 7-Hydroxy-6-phenyl-pyridino [4,3-d][1,3] dioxin (III) | Yield % | m.p. C° | Molecular Formula | Analysis Found C | H | N | Required C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. | $CH_3$- | $C_2H_5$- | 3.0 | 0.9g/30ml | 20-ethyl-2-methyl-7-hydroxy-6-phenyl-pyridinodioxin | 80 | 210 | $C_{16}H1_{15}NO_5$ | 63.8 | 4.8 | 4.5 | 63.8 | 4.9 | 4.6 |
| 2. | $CH_3$- | $C_6H_5$- | 3.5 | 0.9g/30ml | 7-hydroxy-2-methyl-2, 6-diphenyl-pyridinodioxin | 84 | 124 | $C_{20}H_{15}NO_5$ | 68.8 | 4.1 | 4.4 | 68.7 | 4.9 | 4.0 |
| 3. | $C_2H_5$- | $C_6H_5$- | 3.6 | 1.0g/30ml | 2-ethyl-7-hydroxy-2,6-diphenyl-pyridinodioxin | 42 | 159 | $C_{21}H_{17}NO_5$ | 69.6 | 4.6 | 3.7 | 69.9 | 4.6 | 3.8 |
| 4. | $CH_3$- | p-Cl-$C_6H_4$- | 3.8 | 1.0g/30ml | 2-(chlorophenyl)-7-hydroxy-2-methyl-6-phenyl-pyridinodioxin | 57 | 146 | $C_{20}H_{14}NO_5Cl$ | 62.7 | 3.3 | 3.4 | 62.5 | 3.6 | 3.6 |
| 5. | $CH_3$- | $CH_3(CH_2)_3$- | 3.5 | 0.9g/20ml | 2-butyl-7-hydroxy-2-methyl-6-phenyl-pyridinodioxin | 65 | 157 | $C_{18}H_{19}NO_5$ | 65.7 | 5.4 | 4.2 | 65.6 | 5.7 | 4.2 |
| 6. | $C_2H_3$- | $CH_3(CH_2)_2$- | 3.5 | 0.9g/20ml | 2-ethyl-7-hydroxy-6-phenyl 2-propyl-pyridinodioxin | 63 | 158 | $C_{18}H_{19}NO_5$ | 65.8 | 5.7 | 4.1 | 65.6 | 5.7 | 4.2 |
| 7. | $C_3H_2$- | $C_3H_7$- | 3.5 | 0.9g/20ml | 7-hydroxy-6-phenyl-2,2-dipropyl-pyridinodioxin | 46 | 245 | $C_{19}H_{21}NO_5$ | 66.3 | 6.0 | 4.1 | 66.4 | 6.1 | 4.1 |

TABLE 4. UV AND IR SPECTRA OF PYRIDINO [4,3,-d][1,3] DIOXIN (III)

| No. | Pyridino [4,3-d][1,3]-dioxin(III) | | UV Light absorption 95% MeOH | | IR Absorption max $cm^{-1}$ mainly for the 3-6 μ region (KBr disc) | |
|---|---|---|---|---|---|---|
| | R' | R" | $\lambda_{max}$(nm) | Logε | C-O(4)($cm^{-1}$) | C-O(5)($cm^{-1}$) |
| 1. | $CH_3$- | $C_2H_5$- | 310 | 3.90 | 1700 | 1650 |
| 2. | $CH_3$- | $C_6H_5$- | 310 | 4.26 | 1700 | 1655 |
| 3. | $C_2H_5$- | $C_6H_5$- | 312 | 4.21 | 1705 | 1660 |
| 4. | $CH_3$ | p-$ClC_6H_4$- | 310 | 4.79 | 1700 | 1650 |
| 5. | $CH_3$- | n-$C_4H_9$- | 310 | 4.06 | 1723 | 1668 |
| 6. | $C_2H_5$- | n-$C_3H_7$- | 308 | 4.33 | 1702 | 1662 |
| 7. | n-$C_3H_7$- | n-$C_3H_7$- | 310 | 4.29 | 1705 | 1655 |

nylamino)-4,5-dioxo-pyrano[4,3-d][1,3] dioxins (II) which underwent the phenoxide rearrangement to yield the corresponding2,2-disubstituted-7-hydroxy-4,5-dioxo-6-phenylpyridino[4,3-d] [1,3] dioxins (III). Thus the compound 2-ethyl-2-methyl-4, 5-dioxo-7-(phenylamino) pyrano [4,3-d] [1,3]dioxin (II, R'=$CH_3$, R"= $C_2H_5$) on the reaction with sodium phenoxide in phenol gave an enolic product $C_{16}H_{15}NO_5$ (III, R"=$CH_3$, R"=$C_2H_5$) m.p. 210°C, which dissolved in aq. $NaHCO_3$ and was isomeric with the starting material. Other 7-(phenylamino)-pyranodioxins (II) gave similar isomeric products (III).

These pyridinodioxins (III) absorbed characteristically in the UV region 308-312nm (Table 4). The IR absorption peak due to the ester carbonyl group at position 4 appeared at 1700-1725 $cm^{-1}$ which is apparently unbonded, while the peak due to carbonyl at position 5 appeared at 1650-1670 $cm^{-1}$. This is in concordence with the study of IR spectra of similar compounds carried out by Saleh and Hammad [13,14]. Treatment of the product (III, R'=$CH_3$, R"=$C_4H_9$) with diazomethane in chloroform having $\lambda_{max}$ 308nm gave a negative $FeCl_3$ test.

The OH group of the pyridinodioxin (III, R'=$C_2H_5$, R"=$C_3H_7$) reacts with $POCl_3$ to yield the corresponding chloro derivative (IV) $C_{12}H_{13}O_5Cl$, m.p. 160°C having UV absorption at $\lambda_{max}$ 324nm which shows a shift of 12nm towards the visible region as compared with the parent compound.

Bromination of the compound (III, R'=$C_2H_5$, R"=$C_6H_5$) with bromine in chloroform yielded the bromo derivative (V) $C_{21}H_{16}NO_5Br$, m.p. 124°C showing a UV absorption $\lambda_{max}$ at 312nm.

These 7-hydroxy pyridinodioxins also formed addition products with morpholine. For instance, the product (III, R'=$C_2H_5$, R"=$C_3H_7$) when reacted with morpholine gave an adduct with molecular formula $C_{22}H_{28}N_2O_6$, m.p. 193°C, $\lambda_{max}$ 311nm which was soluble in water and which could be converted to the parent compound by the acidification of its aqueous solution.

## References


1. Chichibabin, Bull. Soc. Chim. France, **4**(5), 1326 (1937).
2. R.L. Frank, J. R. Blengen, R. J. Dearborn, R. L. Meyers and F. E. Woodward, J. Am. Chem. Soc., **68**, 1368 (1946).
3. Durikopf and Gollsch, Ber., **23**, 1110 (1890).
4. R. M. Acheson (Ed), "*An Introduction to the Chemistry of Heterocyclic Compounds*, (John Wiley & Sons, New York, 1976), 3rd ed. pp. 271-272.
5. French Patent, 1,339, 175, Assigned to J.R. Giegy, S. A. (1963).
6. J. D. Crum and C. H. Fuchsman, J. Heterocycl. Chem., **3**, 252 (1966).
7. R. Albrecht and G. Kresze, Chem. Ber., **98**, 1431 (1965).
8. T. B. Windholz, L. H. Peterson and G. J. Kent, J. Org. Chem., **28**, 1443, (1963).
9. G. Stork, M. Ohashi, H. Kamashi and H. Hakisawa, J. Org. Chem., **36**, 2784 (1971).
10. S. J. Davis and J. A. Elvidge, J. Chem. Soc., 4109 (1962).
11. M. A. Butt, R. Kemal, A. Salam and A. Akhtar, Pak. j. sci. ind. res., **33**(1-2), 27 (1990).
12. M. A. Butt, R. Kemal, A. Salam and Ghazala Mumtaz, Pak. j. sci. ind. res., **35** (9), 325 (1992).
13. R. M. Saleh, H. M. Baker and O. E. A. Mustafa, Pak. j. sci. ind. res., **34**, 417 (1991).
14. M. M. Hammad, S. A. Said, A. F. El-Farargy and G. M. El-Gendy, Pak. j. sci. ind. res., **36**, (6-7), 228 (1993).