CHAPTER-3

BROMINATION OF XANTHONES

THEORETICAL

BROMINATION OF XANTHONES

The present work deals with some substitution reactions of xanthones and hence the previous work on substitution in simple and hydroxy xanthones is reviewed here.

1. Halogenation :

Flourination: No direct flourination is known in the case of xanthones, however, some of the fluoro xanthones have been synthesised indirectly. Allen et al.[1] have prepared all the four monofluoroxanthones starting from the monofluorophenols and also by Balz-Scheinmann reaction from the corresponding aminoxanthones. Many fluoroxanthones such as octafluoroxanthone[2], 2-Fluoro xanthone[3], 6-Fluoro-2-methoxyxanthone[5], 2,7-difluoroxanthone[4], 6-bromo-2-fluoroxanthone[5] and 1,2,3,4-tetrafluoroxanthone[6] have also been synthesised.

Chlorination: Chlorination of simple xanthone in acetic acid at 110°C in the presence of iodine give mainly 2,7-dichloroxanthone[7]. A highly halogenated product such as octachloroxanthone may be obtained with antimony pentachloride[8]. Hall and Plant[9] have chlorinated 1,2,3,4-tetra hydroxanthone and 7-methyl-2,3,4-tetra-hydroxanthone with chlorine in carbon tetrachloride and obtained the 10,11-

dichloro hexahydroxanthone derivatives. Recently Jayalaksmi et al[10]. have chlorinated 1,3,6-trimethoxy-8-methylxanthone and obtained 1,3,6-trimethoxy-2,4,5,7-tetrachloro-8-methylxanthone. Santesson and Sundholm[11], on chlorination of 1,3,6-trihydroxy-8-methylxanthone with lesser amount of chlorine than the required for the tetrachloro, obtained a mixture containing 1,3,6-trihydroxy-2,4,7-trichloro-8-methyl and 1,3,6-trihydroxy 2,4-dichloro-8-methylxanthone. Kurduker and Subba Rao[12] have chlorinated 3,6-dihydroxyxanthone with sulphuryl chloride and obtained 3,6-dihydroxy-2,4,5,7-tetra-chloroxanthone. No other work on direct chlorination of xanthones appears to have been reported. A number of chloroxanthones have also been synthesised by other methods[13-17].

Bromination: When xanthone in acetic acid is heated with one mole of bromine and a trace of iodine, 3-bromo xanthone is obtained[18] but when conc. sulphuric acid is used as a solvent instead of acetic acid, the product is 2-bromoxanthone. Each of these bromo compounds when treated with bromine passes easily into the same 2,7-dibromo derivative. When temperature and amount of bromine are increased, tetrabromo- and hexabromoxanthone are formed but the structures have not been determined.

Although xanthone is brominated in sulphuric acid solution by liquid bromine, it is not attacked by the mixture of potassium bromide and potassium bromate in sulphuric acid[19]. 2,7-Dibromoxanthone was obtained by brominating xanthone[20]. Bromination of 3,6-dihydroxy xanthone gave 3,6-dihydroxy-2,4,5,7-tetrabromoxanthone[12]. Most of the bromoxanthones have been made by synthetic means or from amino derivatives or by mercuration followed by bromination[21].

The insecticidal properties of xanthones and their derivatives were reported by a number of workers[22-25]. Some of the bromoxanthones have been found to possess urinary antiseptic activity[26] and 3-bromoxanthone and 2,7-dibromoxanthone are used in insecticidal preparations. Halo and nitro derivatives of some hydroxy and methoxy xanthones have been reported as potential insecticides[12].

Bromoxanthones are synthesised by direct bromination of xanthones or by application of Sandmeyer reaction on amino xanthone or by mercuration followed by bromination[21]. Koning and Kostancki[27], reported the synthesis of dibromo derivative of 1-hydroxy-, 2-hydroxy-, 3-hydroxy-, 4-hydroxy and 1,7-dihydroxyxanthone using bromine in acetic acid as a brominating agent, the structural assignment for dibromoxanthone has not been done by them.

Kudukar and Subba Rao[12] reported the synthesis of 2,7-dibromo and 2,4,5,7-tetrabromo-3,6-dihydroxyxanthone by brominating 2,2', 4,4'-tetrahydroxybenzophenone followed by its cyclisation. Condensation of 2-bromoresorcinol with salicylic acid, using $ZnCl_2$ - $POCl_3$ method gave 4-chloro-3-hydroxyxanthone[28] instead of 4-bromo-3-hydroxy xanthone.

It has been observed that no work has been reported so far for the synthesis of monobromohydroxyxanthone hence the present work has been undertaken and it deals with the bromination of some hydroxyxanthones to study the pattern of substitution, to study the insecticidal and herbicidal properties of bromohydroxyxanthones and to utilise bromo derivatives obtained for further synthetical work such as the synthesis of bromo furano xanthones and furanoxanthones.

The bromination of hydroxyxanthones has been studied with two different brominating agents.

(i) bromine in acetic acid

(ii) pyridine hydrobromide perbromide in acetic acid[29]. This reagent is used for the first time for the bromination of xanthones. Using this reagent synthesis of monobromo derivatives can be achieved easily in good yield. Bromination of 3-hydroxyxanthone,

1-hydroxyxanthone, 2-hydroxyxanthone, 1-hydroxy-3-methyl xanthone, 3-hydroxy-4-methylxanthone,

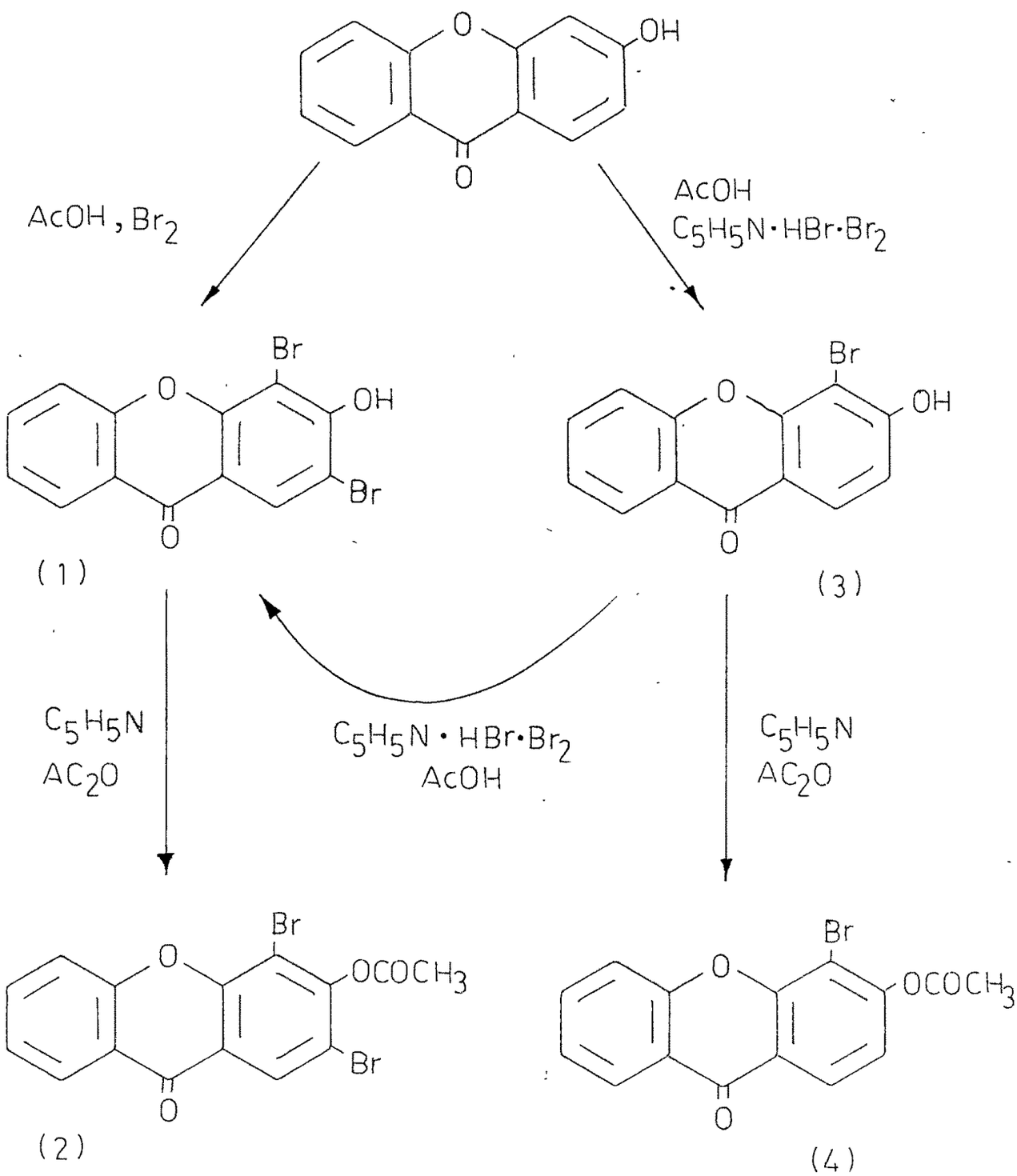
and 3-hydroxy-7-bromoxanthone has now been studied and 7-bromo-1-hydroxyxanthone, 7-bromo-3-hydroxy xanthone, have been prepared by thermal condensation method described earlier in Chapter II. The structure of the bromo compounds have been established by the NMR and mass spectral studies.

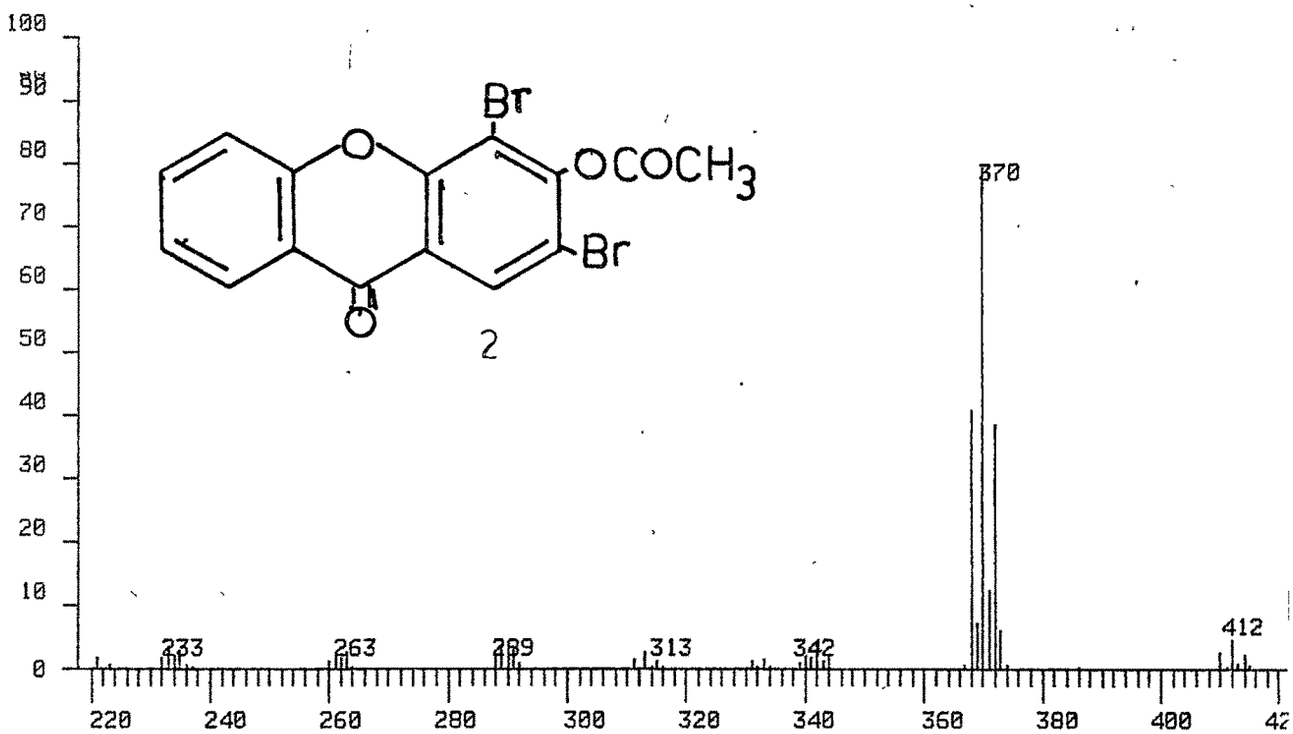
Bromination of 3-hydroxyxanthone

Bromination of 3-hydroxyxanthone with one or less than one or two moles of bromine in acetic acid gave 2,4-dibromo-3-hydroxyxanthone (1) structure of this compound was confirmed by NMR and mass spectra of its acetoxy derivative (2). mass (Chart 1) m/e 414, 412, 410 (M^+, 2.1, 4.2, 2.1) indicating the presence of two bromine in compound (2), the loss of two bromine (Br) was also observed from the molecular ion peak. NMR ($CDCl_3$) (Fig.2) showed only one singlet in the down field aromatic region at δ 8.55, which is assigned to the proton H-1 and double doublet of J=9Hz, 2Hz, centered at δ 8.3 for periproton H-8 indicating that the position two is occupied by bromine. Furthermore it showed peaks at δ 7.78, td, 1H, J=9Hz, H-6; 7.58 d, 1H, J=9Hz, H-5; 7.4, td, 1H, J=9,9,2Hz, H-7; 2.45, s, 3H, $OCOCH_3$ confirms

the assigned structure (2). 3-Hydroxyxanthone on treatment with pyridine hydrobromide perbromide in acetic acid gave 3-hydroxy-4-bromoxanthone (3), structure of which was confirmed by NMR and mass spectra of its acetoxy derivative (4); mass (Fig.3) m/e 334, 332 (M^+) as the intensities of both the peaks are equal, it is clear that this compound contain only one bromine which was further supported by its elemental analysis. After the loss of $-COCH_2$ from molecular ion peak, loss of one bromine was also observed. Furthermore NMR ($CDCl_3$) (Fig.4) showed two doublets of same J value one at δ 8.35, d, J=9Hz, H-1 another at δ 7.18, d, 1H, J=9Hz, H-2 which clearly indicate that position 4 is occupied by bromine and not the position 2, otherwise two singlets could have been obtained in aromatic region. 7.57, d, 1H, J=9Hz, H-5; 7.75, td, 1H, J=9,9,2Hz, H-6; 7.4, td, 1H, J=9,9,2Hz, H-7; 3.0, dd, 1H, J=9,2Hz, H-8; 2.4, s, 3H, $OCOCH_3$ this means that compound (4) is 4-bromo-3-acetoxyxanthone.

4-Bromo-3-hydroxyxanthone on bromination with pyridine hydrobromide perbromide gave 2,4-dibromo-3-hydroxyxanthone(1). The debromination of 2,4-dibromo-3-hydroxyxanthone (1) gave an interesting result, When compound (1) was refluxed in N,N -dimethylaniline for about 30 min. a product was obtained which was characterised as 2-bromo-3-hydroxy xanthone (5) on the basis of mix. m.p. and co TLC with the compound obtained during Claisen migration of 2,4-dibromo-3-


AcOH , Br2
AcOH
C5H5N·HBr·Br2
(1)
(3)
C5H5N
AC2O
C5H5N · HBr·Br2
AcOH
C5H5N
AC2O
(2)
(4)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OCOCH3
Br
2
100
90
80
70
60
50
40
30
20
10
0
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263
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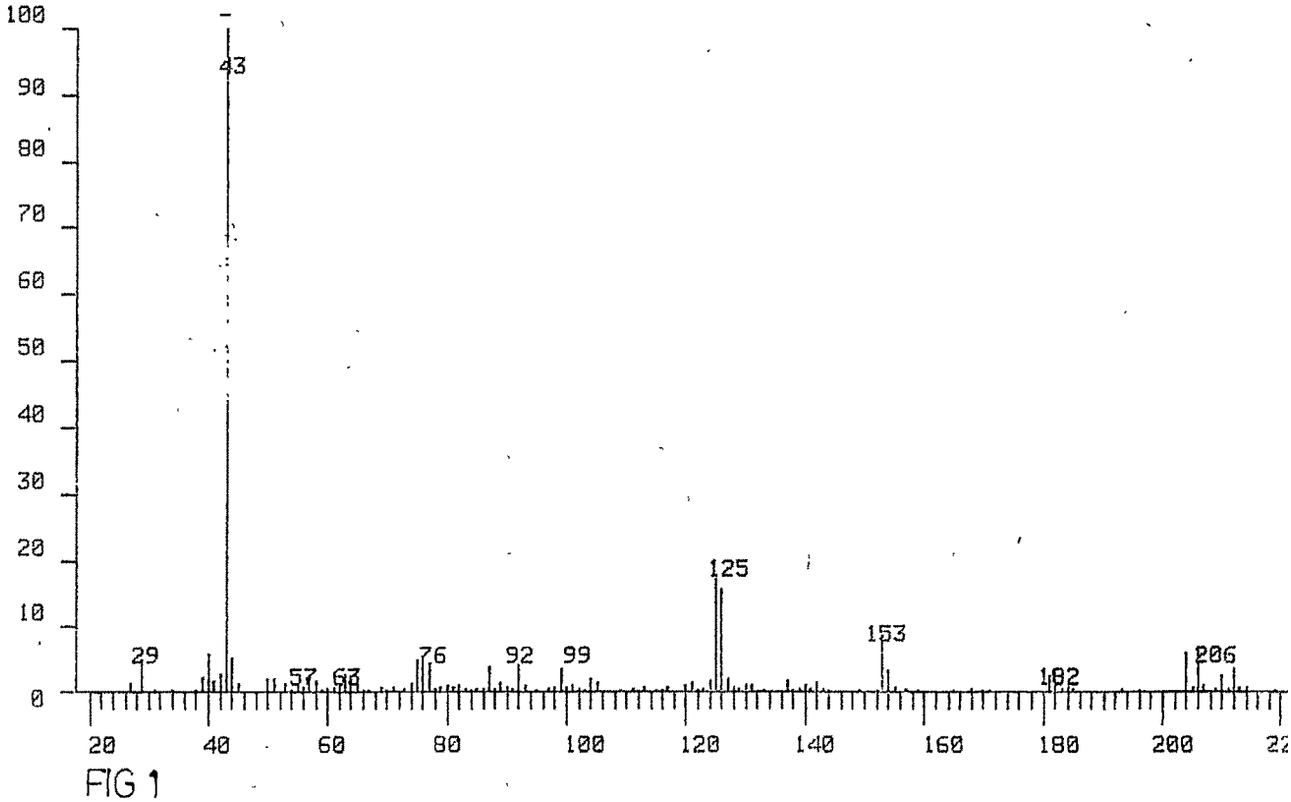
360
380
400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80
70
60
50
40
30
20
10
0
43
29
57
63
76
92
99
125
153
182
206
20
40
60
80
100
120
140
160
180
200

FIG 1

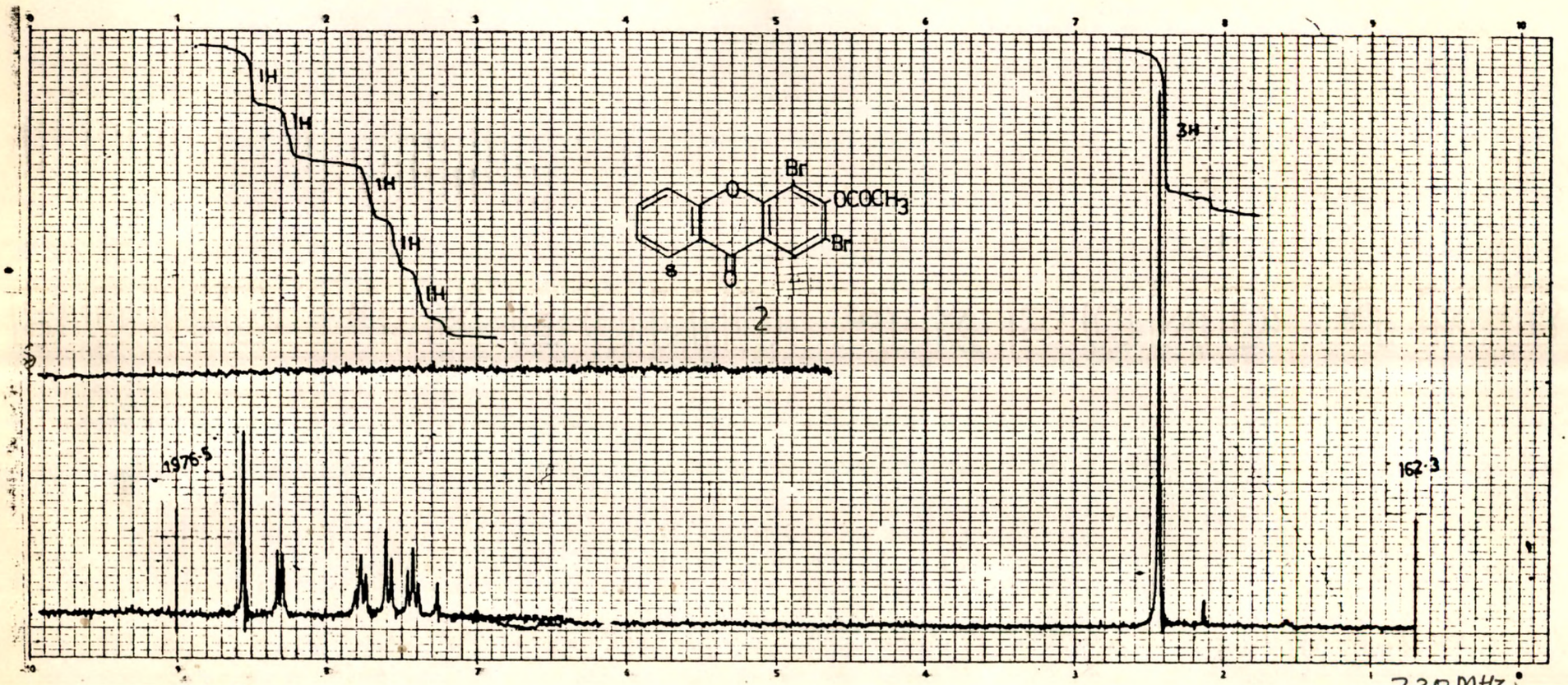
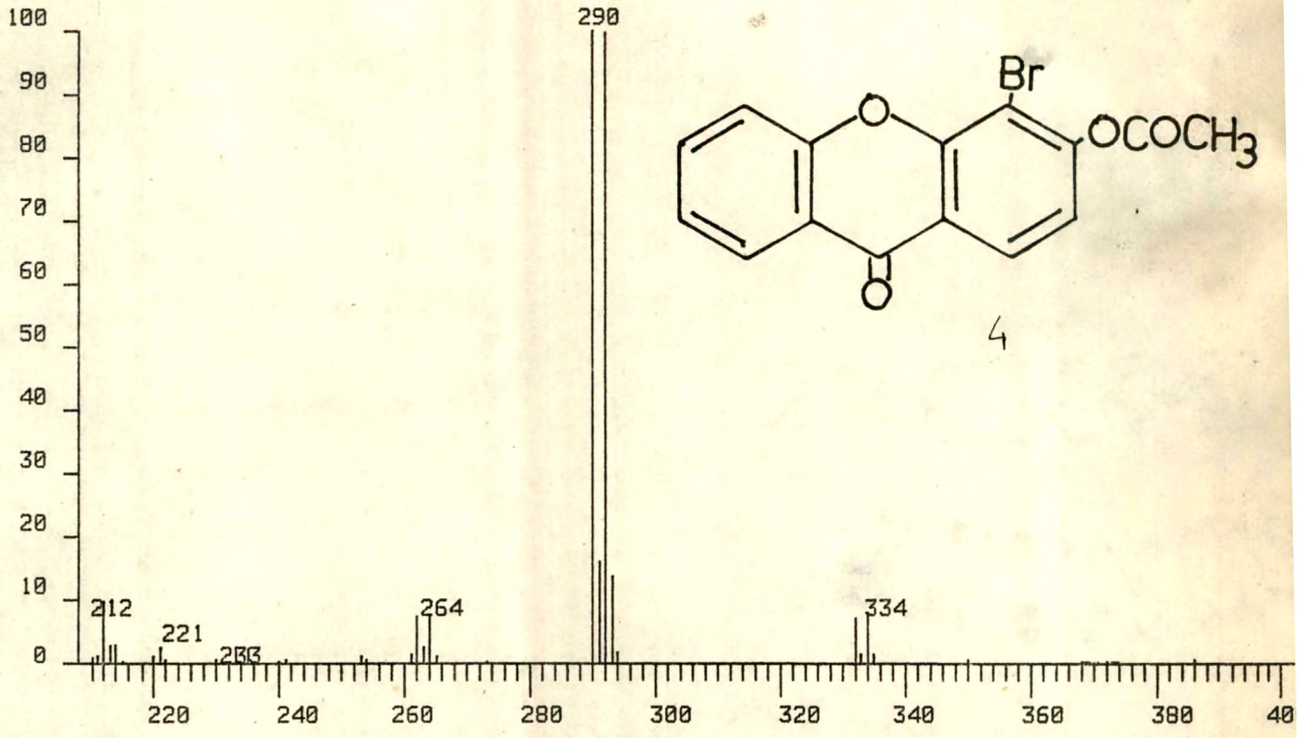


FIG 2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10
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212
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334
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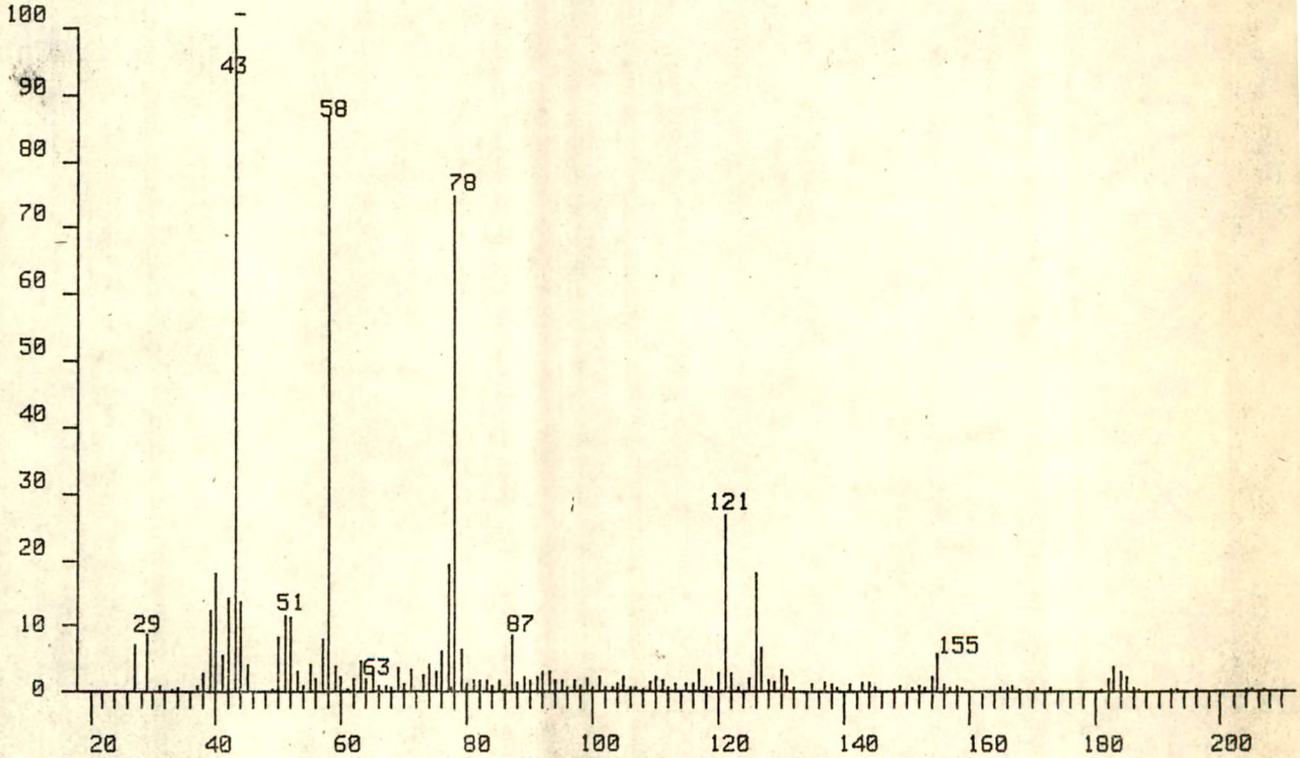
320
340
360
380
Br
OCOCH3
O
O

4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80
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60
50
40
30
20
10
0
43
58
78
121
29
51
87
155
63
20
40
60
80
100
120
140
160
180
200

FIG 3

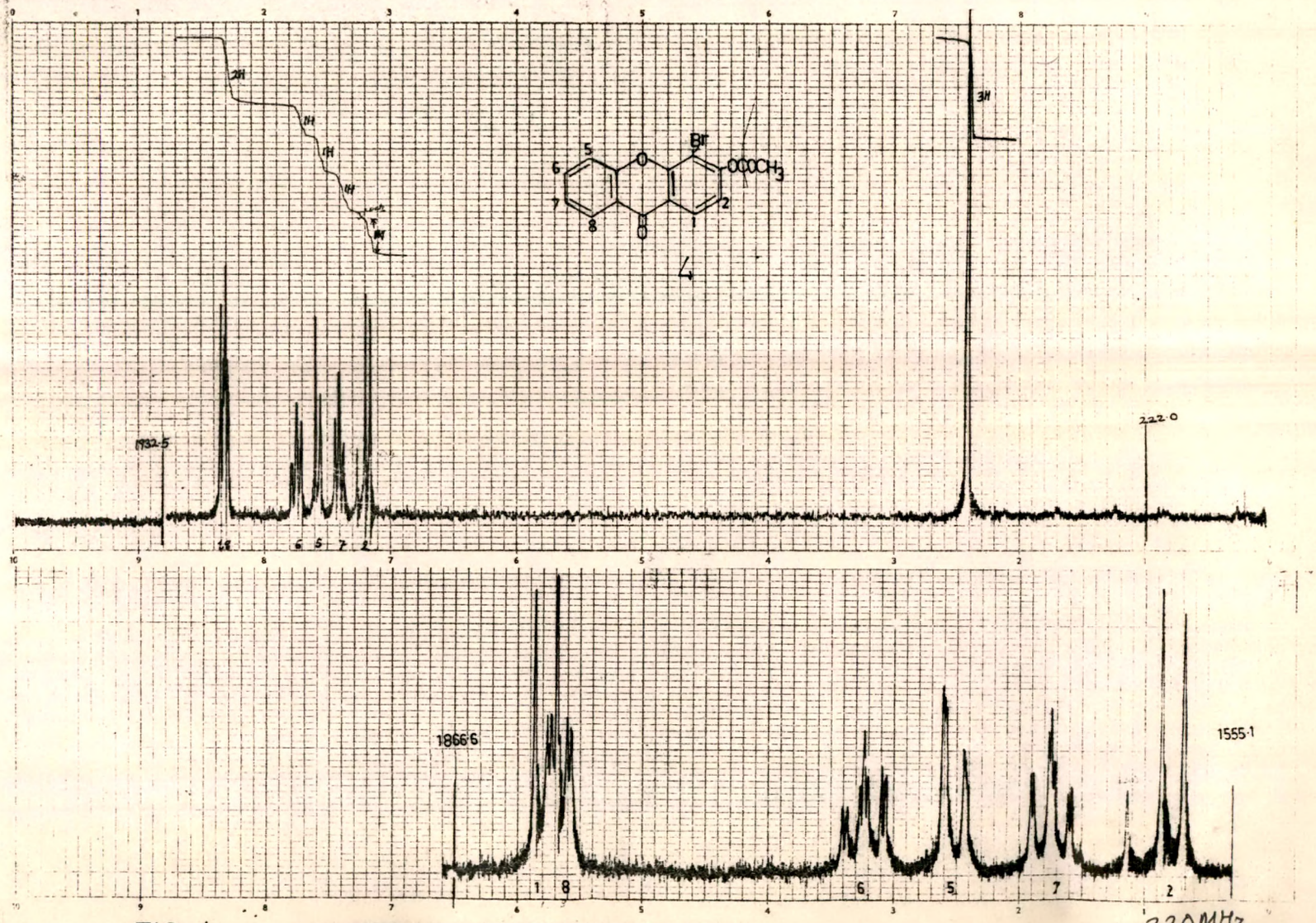
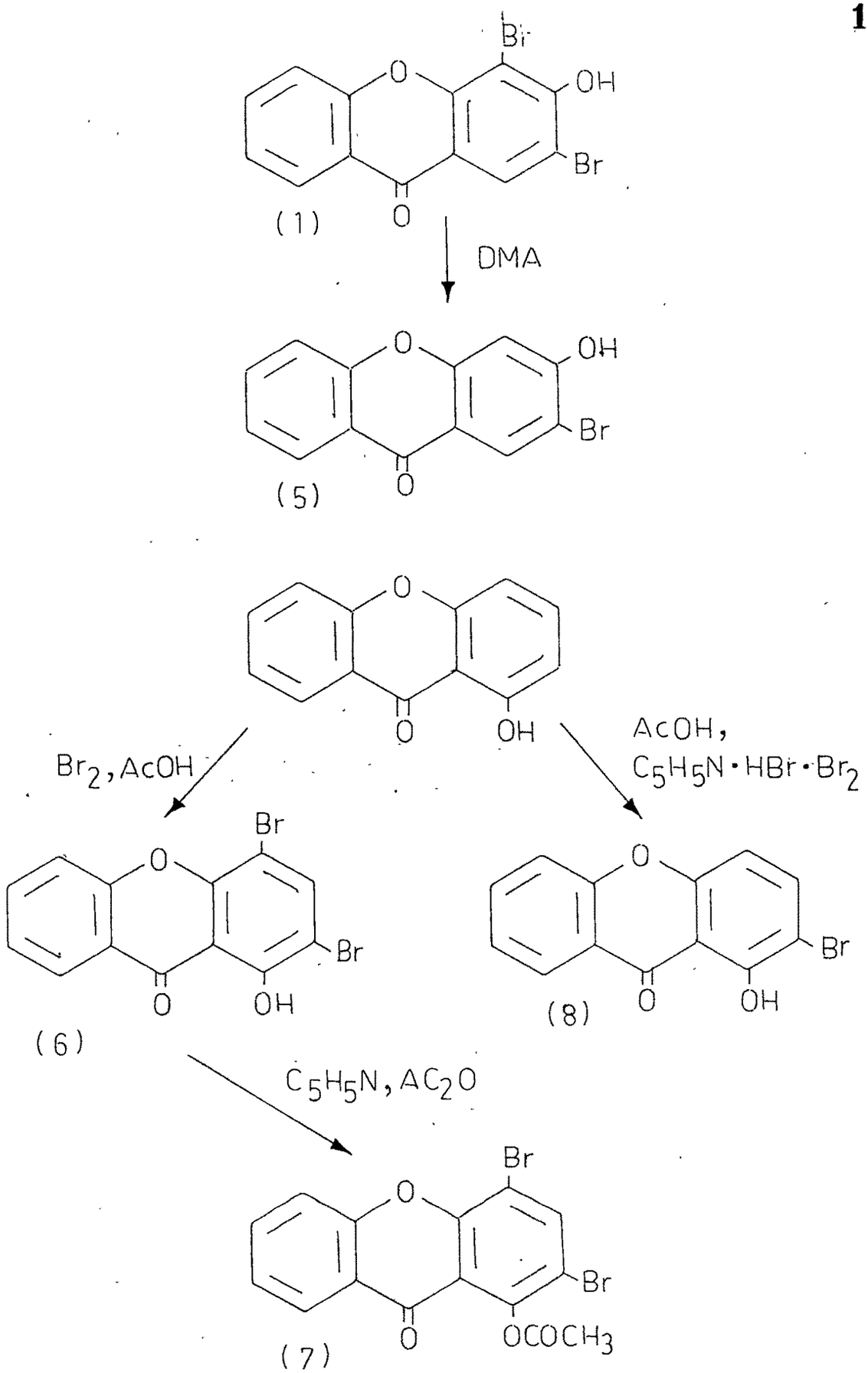


FIG 4

allyloxyxanthone Chapter (4), while compound (1) on refluxing in glacial acetic acid for 10 hr, same compound (1) was obtained without any change. No other method like $ZnCl_2$-$POCl_3$ gave the compound (5) even the thermal condensation of 4-bromoresorcinol with ethyl salicylate gave completely debrominated xanthone instead of expected 2-bromo-3-hydroxyxanthone (5).

Bromination of 1-hydroxyxanthone

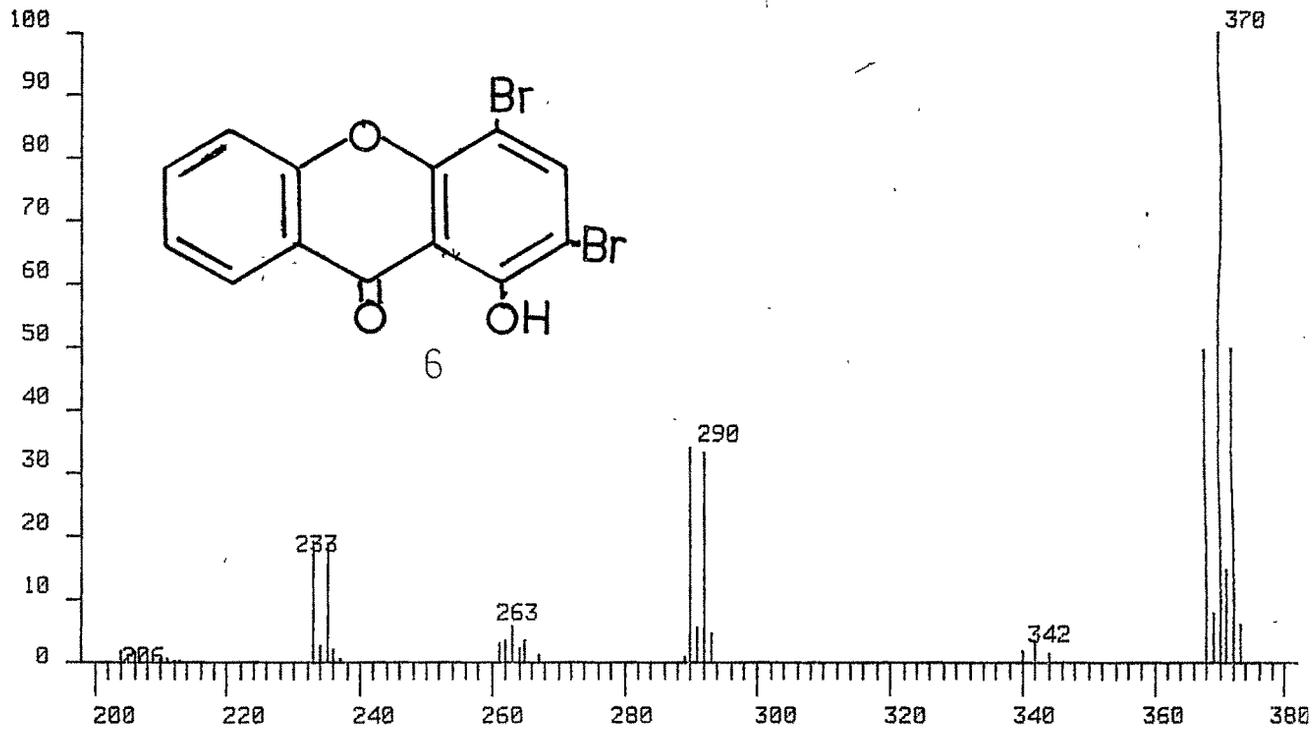
1-Hydroxyxanthone gave 2,4-dibromo-1-hydroxyxanthone (6) with one or two moles of bromine in acetic acid, as the mass spectrum (Fig.5) of the compound (6) showed molecular ion peak at 372, 370, 368 bearing intensity in the ratio of 1:2:1, which is the characteristic pattern of dibromo compound thus indicating the presence of two bromine in the compound (6). This was further supported by the mass fragmation pattern. NMR ($CDCl_3$) (Fig.6) of its acetoxy derivative (7) showed one proton doublet of J value 9Hz centered at δ 8.18 which could be assigned to the periproton H-8 and only one singlet in the down field aromatic region at δ 8.12 which is assigned to proton at position 3 as it is flanked by two bromine. δ 7.7, td, 1H, J=9,9,2Hz, H-6; 7.5, d, 1H, J=9Hz, H-5; 7.35, td, 1H, J=9,9,2Hz, H-7; and 2.6, s, 3H, $OCOCH_3$.


Br
OH
Br
O
O
(1)
DMA
OH
Br
O
O
(5)
O
OH
O
Br2, AcOH
AcOH,
C5H5N·HBr·Br2
Br
Br
O
O
OH
(6)
O
Br
O
OH
(8)
C5H5N, AC2O
Br
Br
O
O
OCOCH3
(7)

Thus confirms the assigned structure (7), while 1-hydroxy xanthone on bromination with pyridine hydrobromide perbromide in acetic acid gave 2-bromo-1-hydroxyxanthone (8) the structure of which was established on the basis of mass and NMR spectral studied. Mass (Fig.7) showed m/e 292, 290 indicating the presence of only one bromine in the compound (8) as the NMR ($CDCl_3$) of it showed a doublet centered at δ 8.4 which could be assigned to only periproton H-8; 7.7 to 7.4, multiplet, 3H, H-5, H-6 and H-7; 6.8, doublet, 1H , proton at position 3; 13.4, singlet, 1H, for -OH group.

Bromination of 2-hydroxyxanthone

Bromination of 2-hydroxyxanthone with one mole or an excess of bromine in acetic acid gave 1,3-dibromo-2-hydroxyxanthone (9), its structure was confirmed by NMR and mass spectra of its acetoxy derivative (10). Mass (Fig.8) m/e 386, 384, 382 indicates the presence of two bromine. NMR ($CDCl_3$) showed a double doublet at δ 8.25 1H, J=9,2Hz meaning that it is an ortho and para coupled peak, more over it is in the down field region so assignments were made for the proton at position 8; 7.7 to 7.4, multiplet, 3H, H-5, H-6 and H-7; 7.3, singlet of one proton at position 4; 2.4, singlet, 3H, $OCOCH_3$. While bromination of 2-hydroxyxanthone with pyridine hydrobromide perbromide gave monobrominated


Br
Br
O
O
OH
6
370
290
233
263
342
206
100
90
80
70
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40
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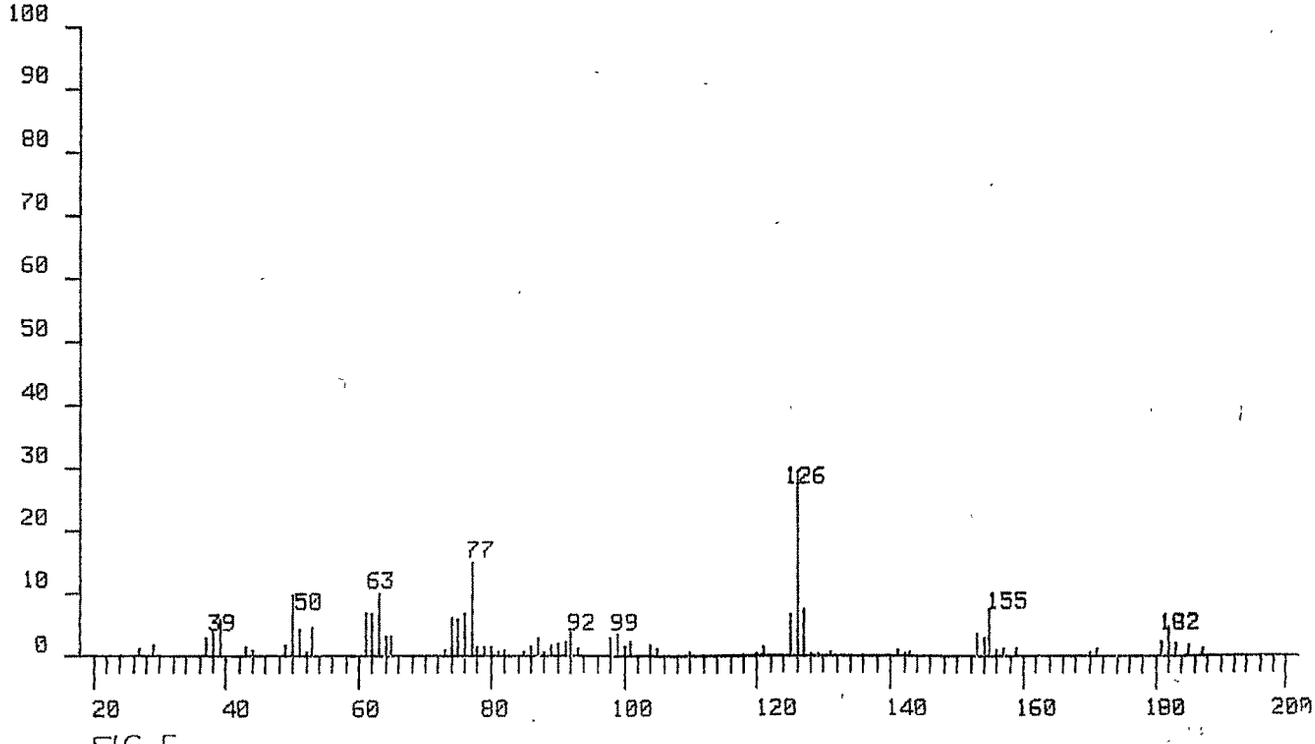
20
10
0
200
220
240
260
280
300
320
340
360
380


126
77
63
50
39
92
99
155
182
100
90
80
70
60
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40
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80
100
120
140
160
180
200

FIG 5

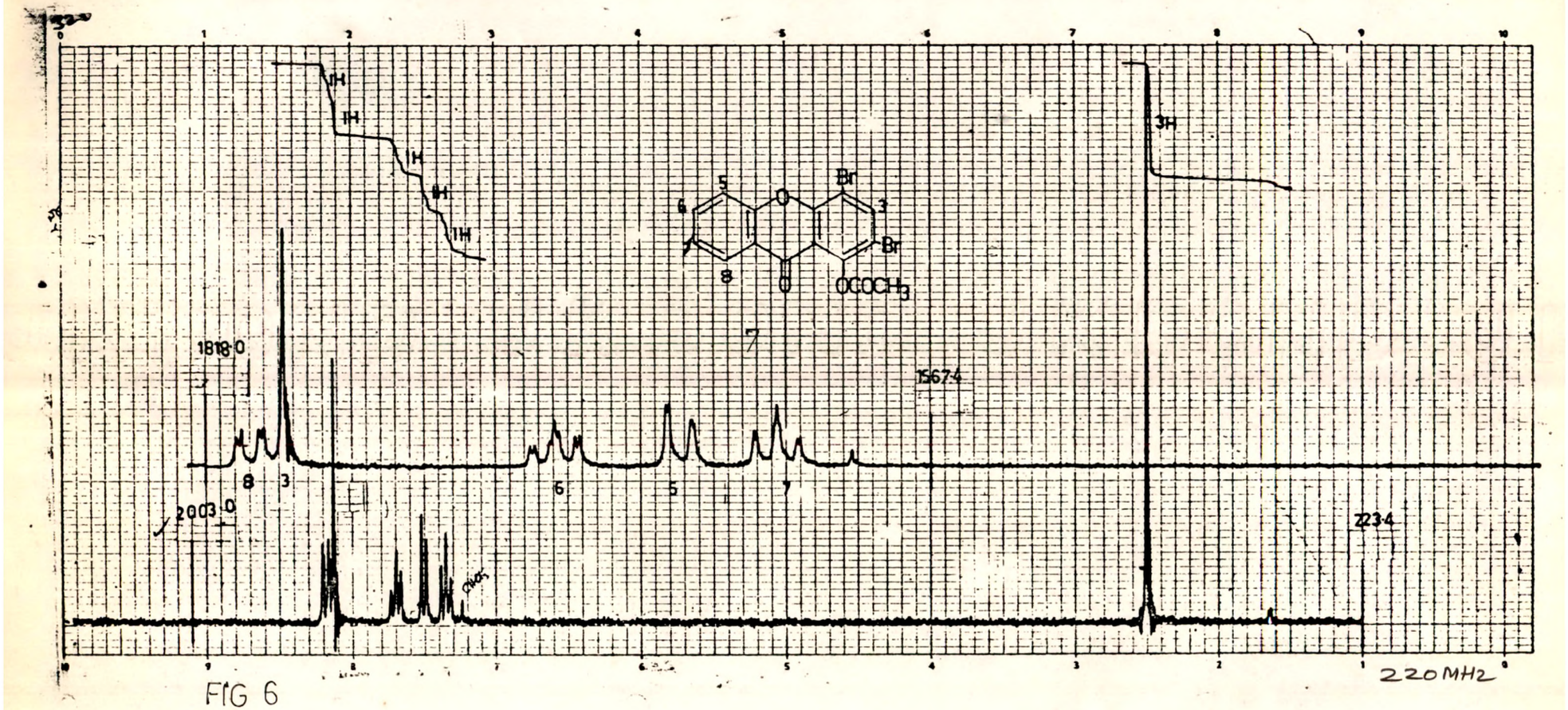
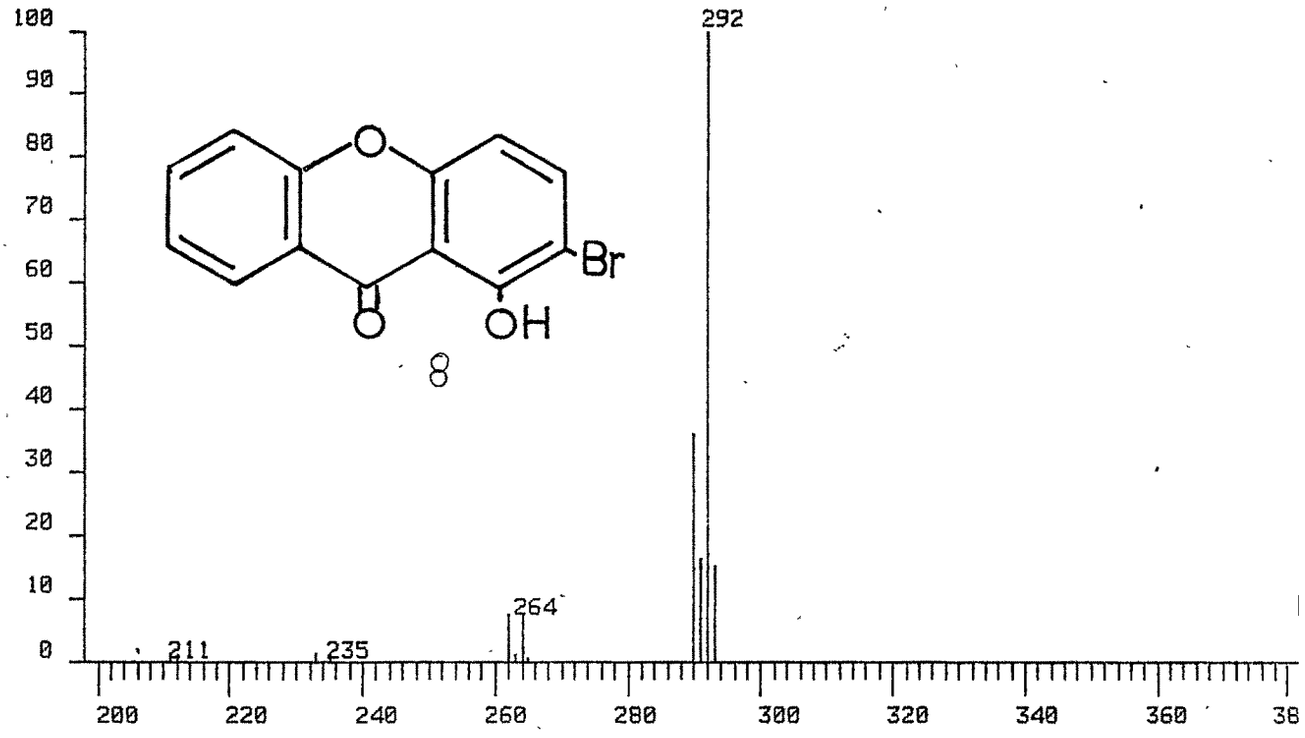

1H
1H
1H
1H
1H
3H
Br
Br
OCOCH3
7
1818·0
2003·0
1567·4
223·4
8
3
6
5
7
220MHz

FIG 6


100
90
80
70
60
50
40
30
20
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292
264
211
235
Br
OH
200
220
240
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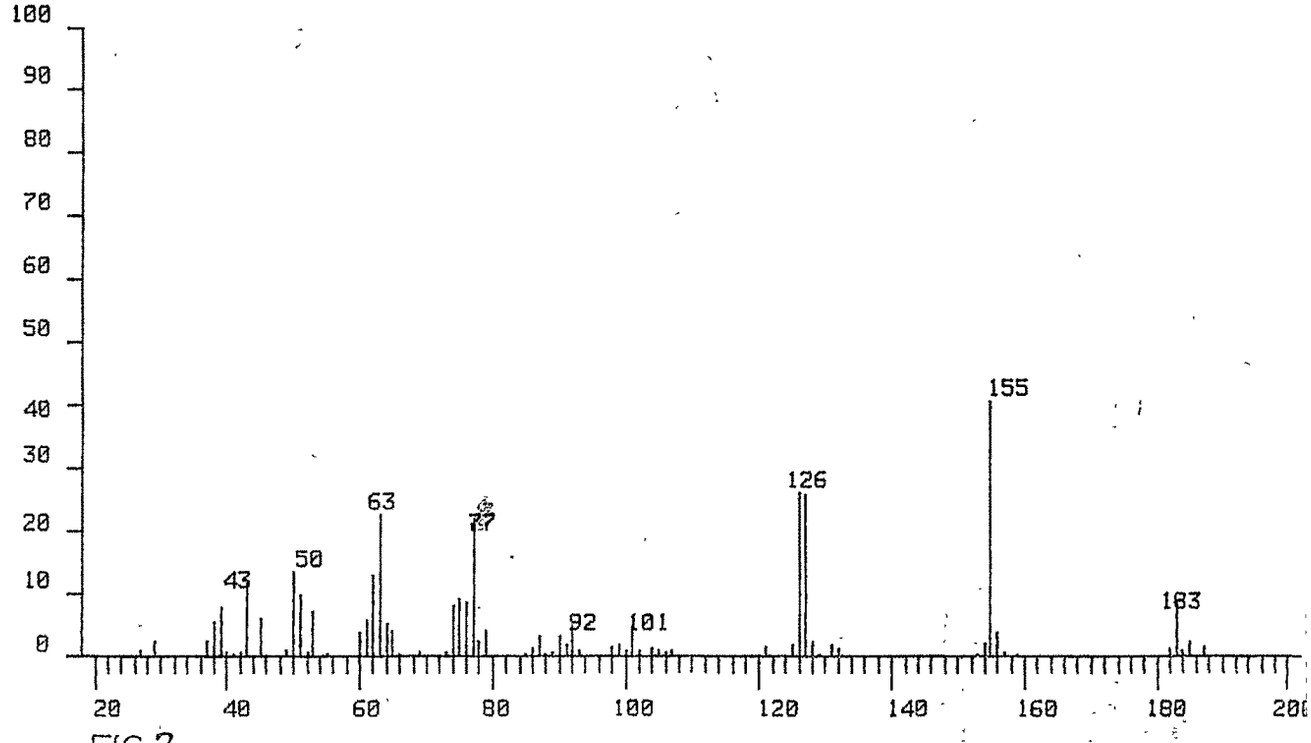
280
300
320
340
360

8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60
50
40
30
20
10
0
155
126
63
77
50
43
92
101
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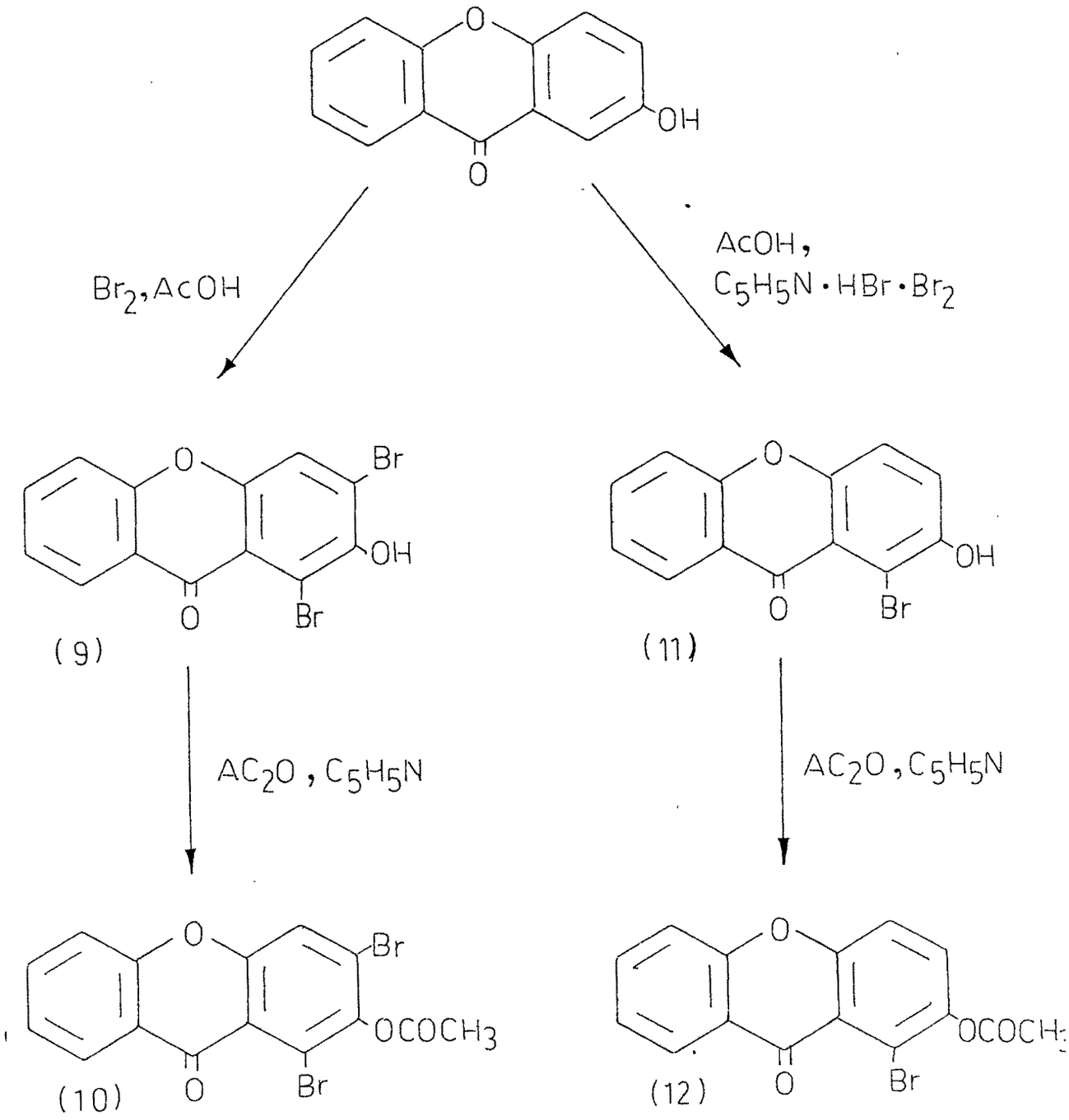
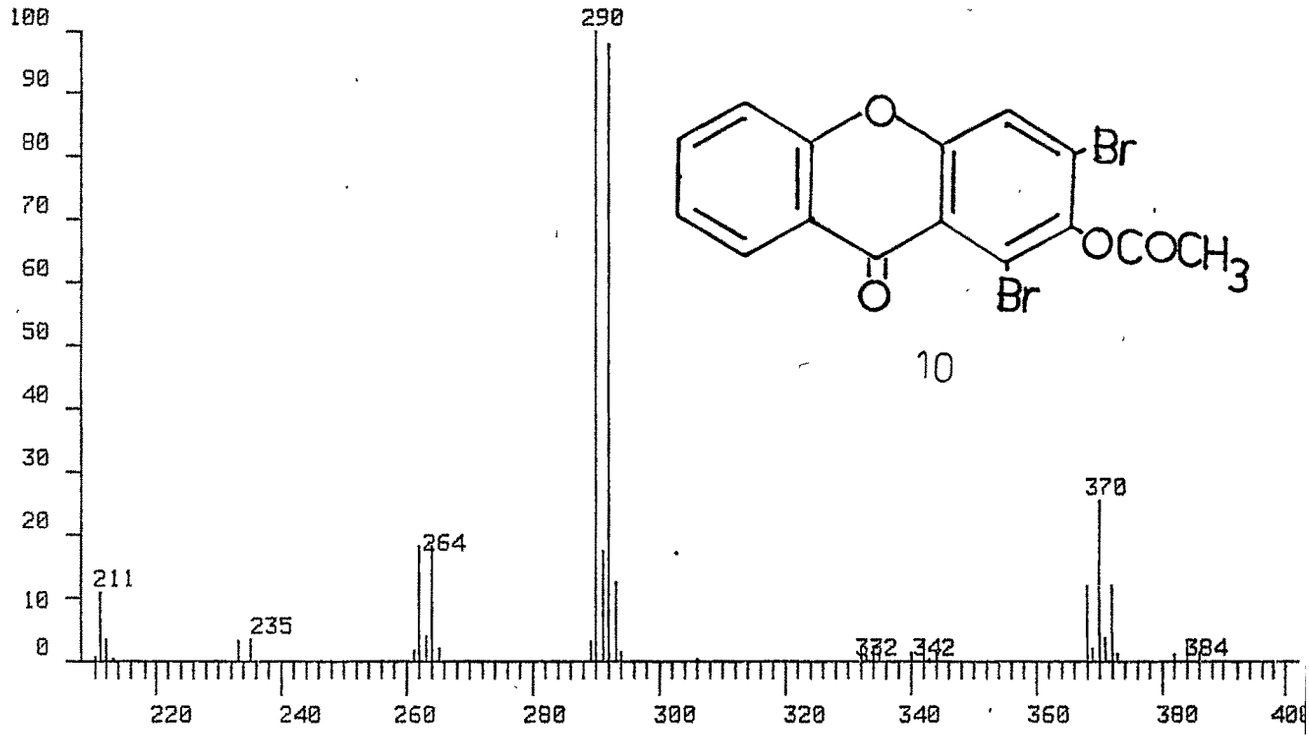
40
60
80
100
120
140
160
180

FIG 7


Br2, AcOH
AcOH,
C5H5N·HBr·Br2
(9)
(11)
AC2O, C5H5N
AC2O, C5H5N
(10)
(12)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264
211
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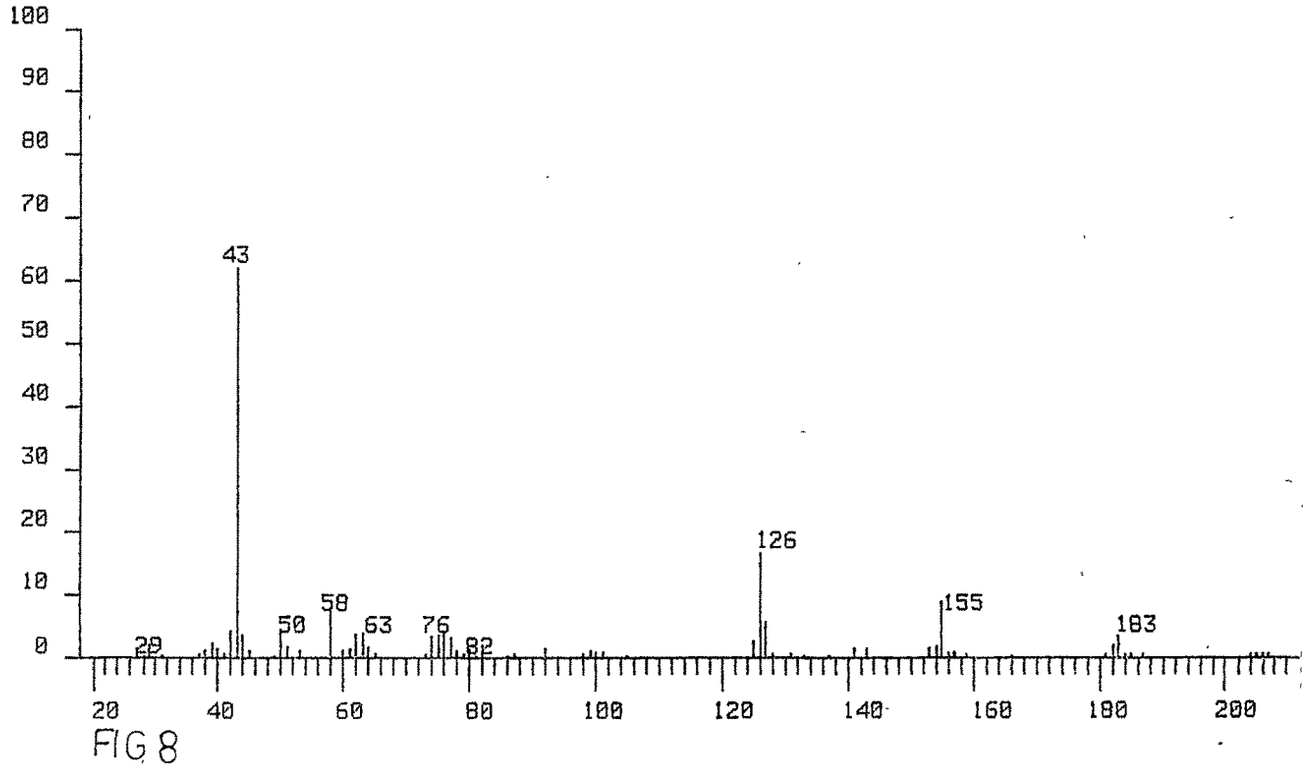
280
300
320
340
360
380
Br
OCOCH3
Br
O
O

10


100
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70
60
50
40
30
20
10
0
43
126
58
155
183
50
63
76
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28
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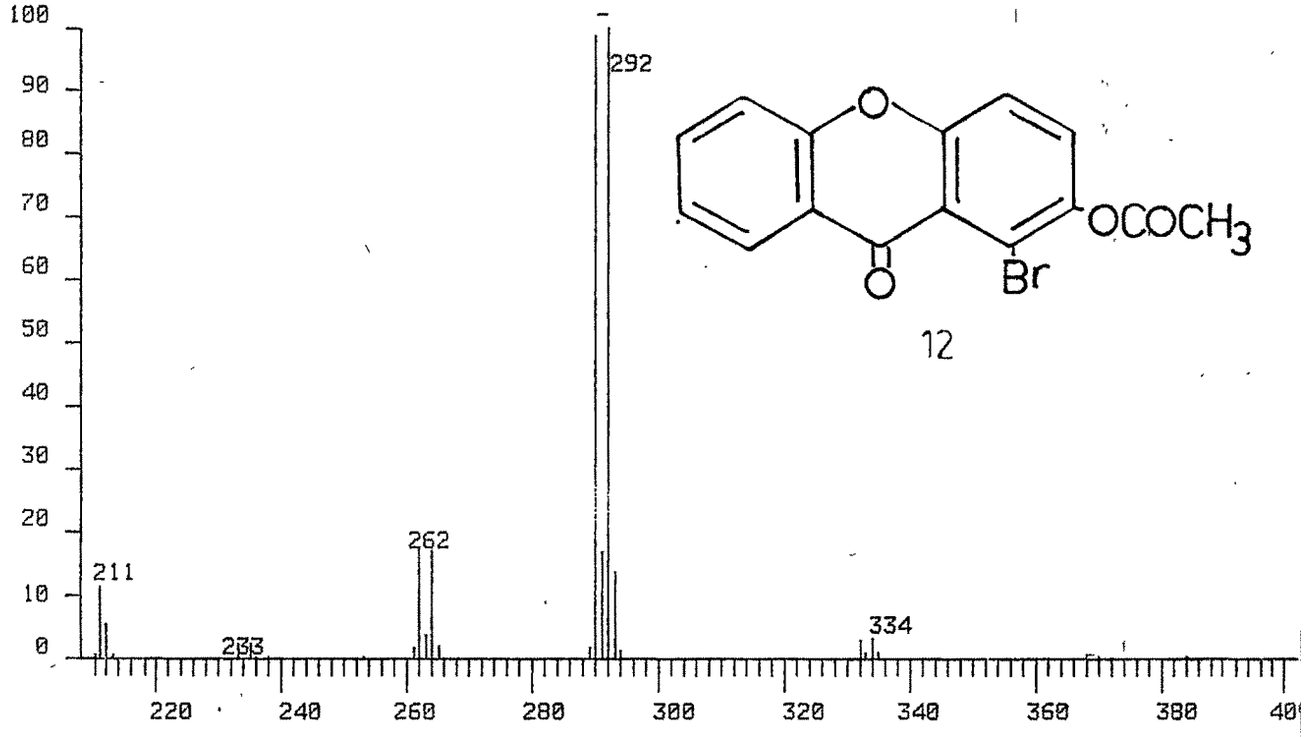
60
80
100
120
140
160
180
200

FIG 8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20
10
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262
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334
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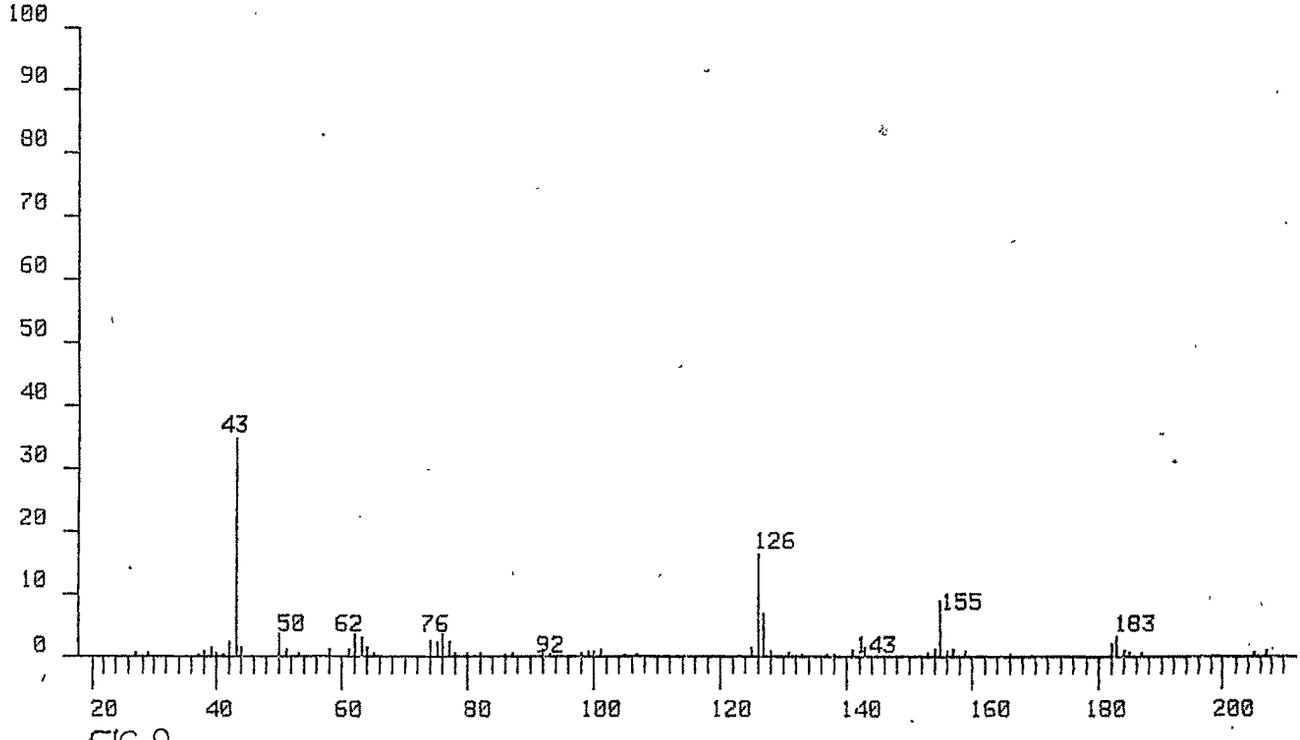
380
OCOCH3
Br
O
O

12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20
10
0
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50
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183
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60
80
100
120
140
160
180
200

FIG 9

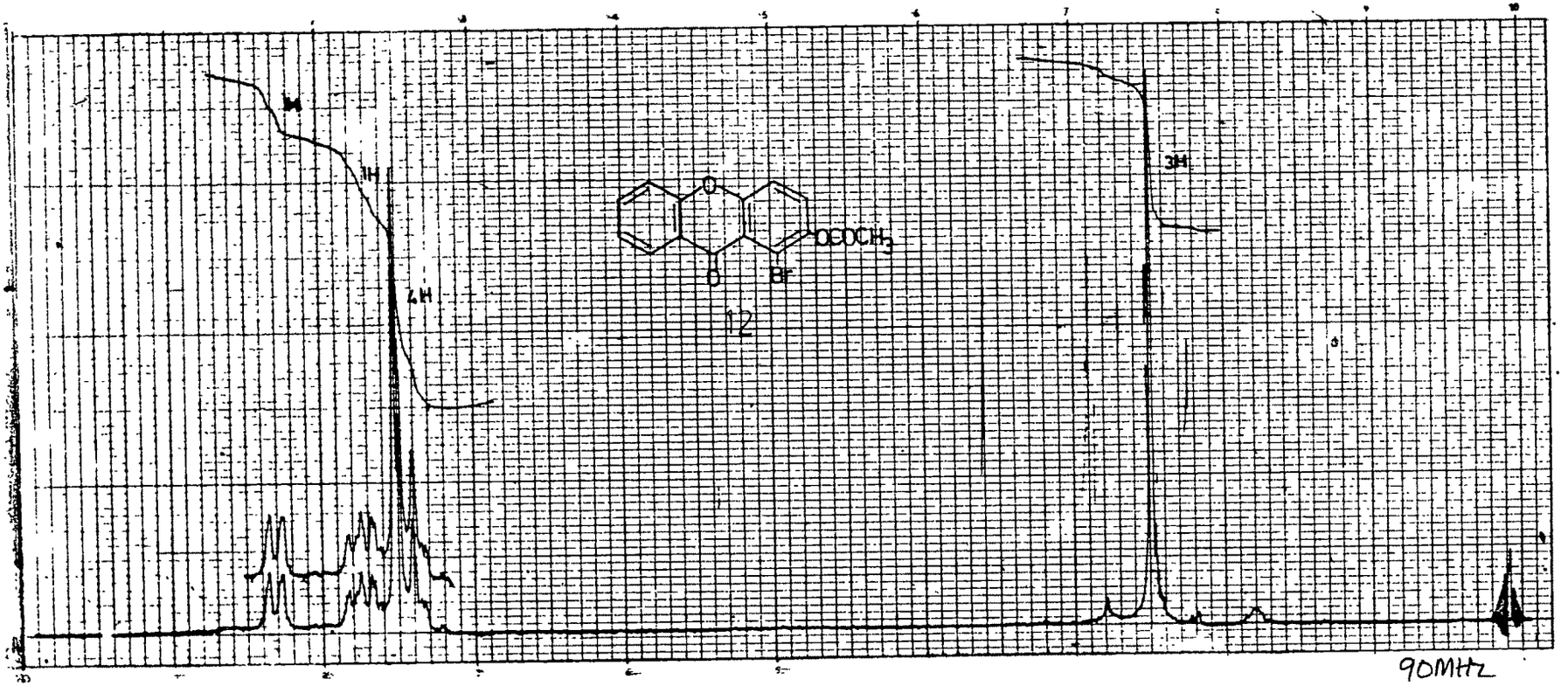
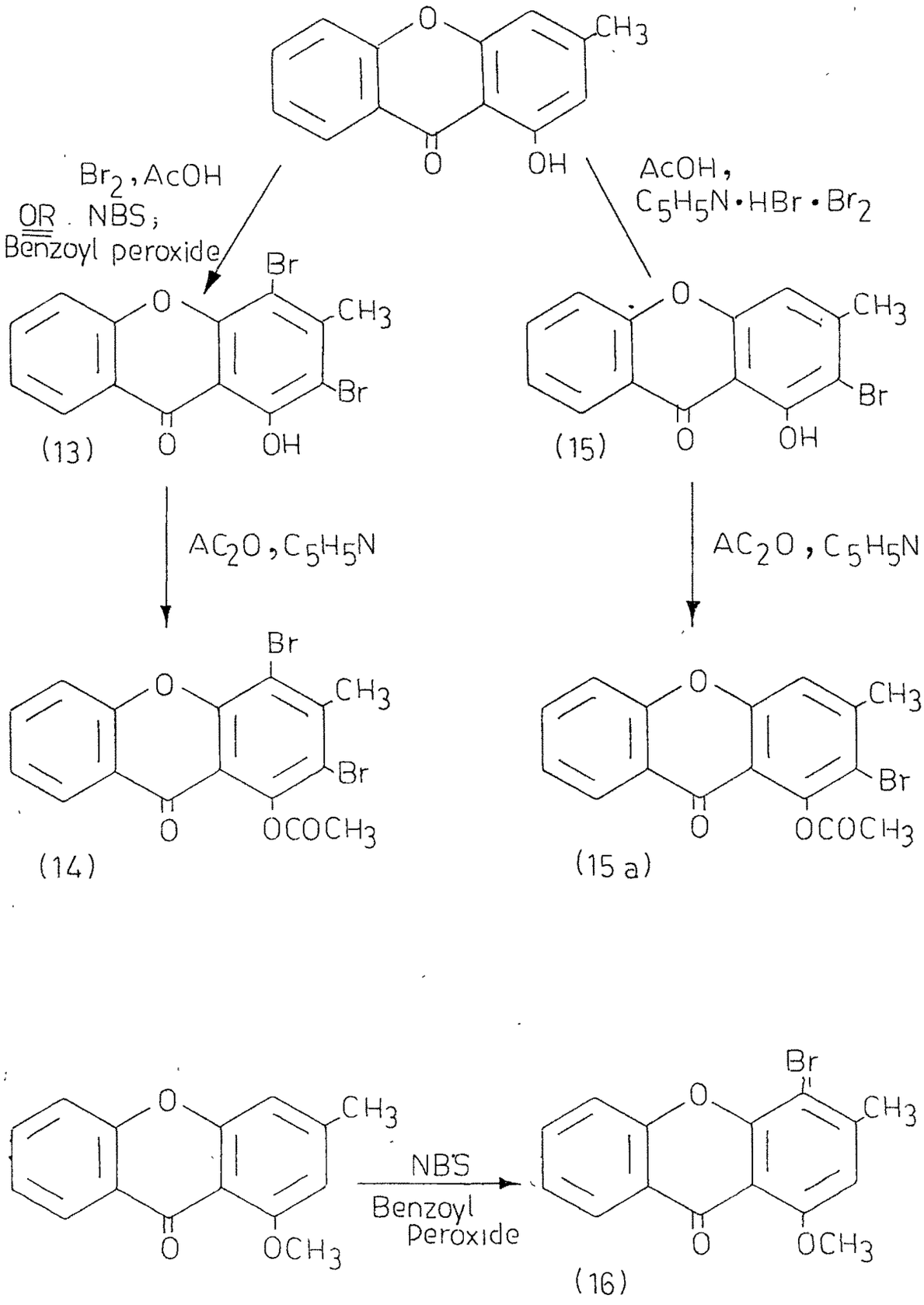


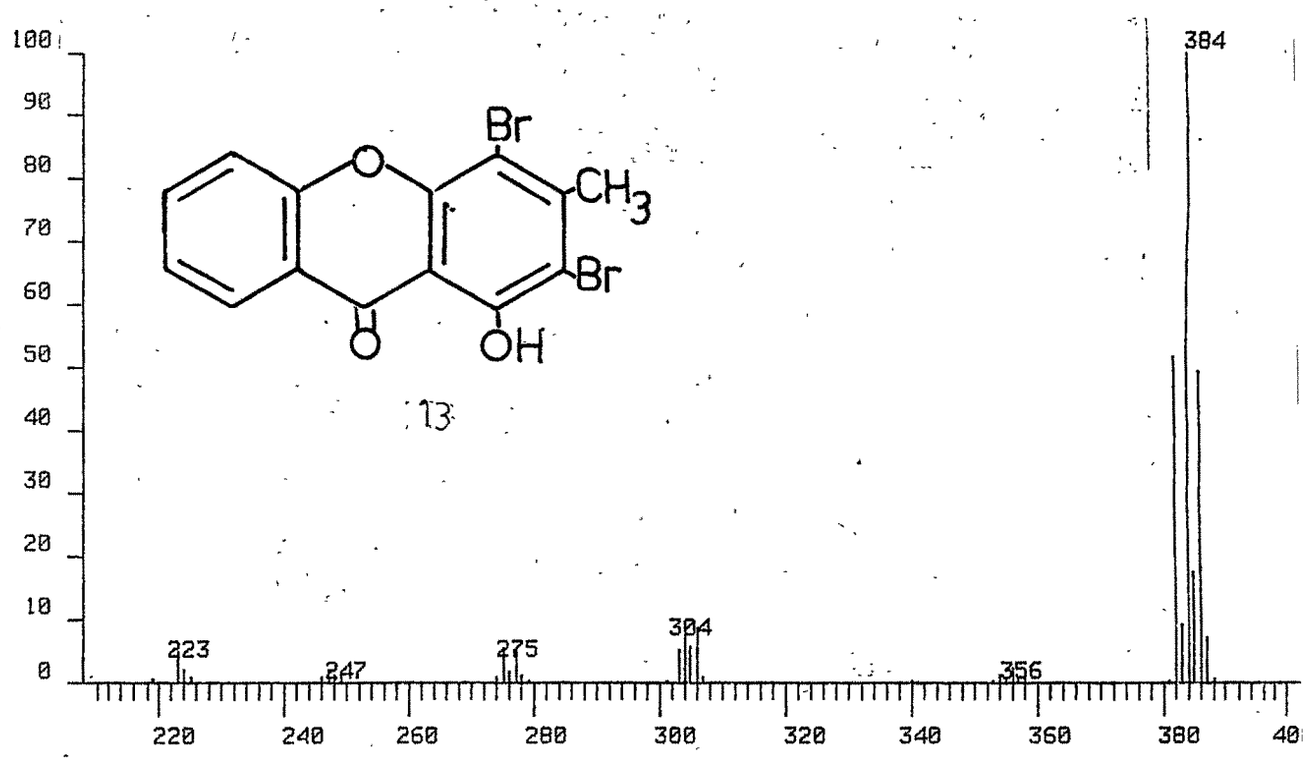
FIG 10

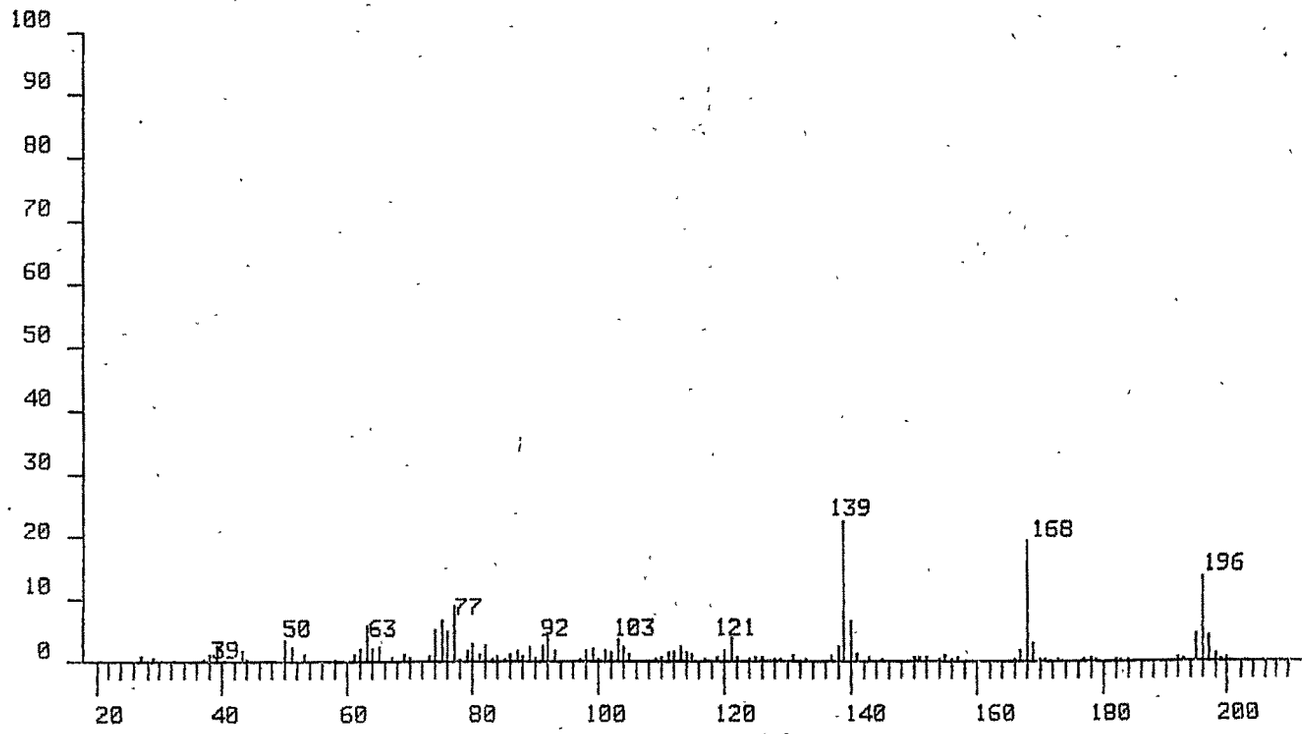
product, 1-bromo-2-hydroxyxanthone (11). Its structure was assigned on the basis of NMR and mass spectral data of its acetoxy derivative (12) mass (Fig.9) m/e 334,332 NMR ($CDCl_3$) (Fig.10) showed a double doublet at δ 8.25 for the proton at position 8; 7.67, td, J=9,9,2Hz, proton at position 6; 7.2 to 7.5, multiplet, 4H, H-3, H-4, H-5 and H-7 and 2.4, singlet, 3H, $OCOCH_3$.

Bromination of 1-hydroxy-3-methylxanthone

Bromination of 1-hydroxy-3-methylxanthone with one or two moles of bromine in acetic acid gave 2,4-dibromo-1-hydroxy-3-methylxanthone (13) which was also obtained when 1-hydroxy-3-methylxanthone was treated with NBS in presence of benzoyl peroxide. It clearly indicates that instead of side chain bromination, nuclear bromination has taken place and that too was an unexpected dibromination. Structure of (13) was confirmed by NMR and mass spectral studies. Mass (Fig.11) m/e 386, 384, 382 (50, 100, 52) suggest that compound is a dibromo derivative. NMR ($CDcl_3$) (Fig.12) of its acetoxy derivative (14) showed δ8.22, double doublet, J=9, 1.5Hz (ortho meta coupling) this peak could be assigned to the proton at position 8 as it is ortho to carbonyl group, 7.8 to 7.29, multiplet of the remaining three aromatic protons H-5, H-6 and H-7; 2.88, S, 3H, $ArCH_3$, 2.58, singlet, 3H, $OCOCH_3$ thus confirms the


Br2, AcOH
OR NBS;
Benzoyl peroxide
AcOH,
C5H5N·HBr·Br2
(13)
(15)
AC2O, C5H5N
AC2O, C5H5N
(14)
(15 a)
NBS
Benzoyl
Peroxide
(16)


Br
CH3
Br
O
OH
O
13
100
90
80
70
60
50
40
30
20
10
0
223
247
275
304
356
384
220
240
260
280
300
320
340
360
380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90
80
70
60
50
40
30
20
10
0
39
50
63
77
92
103
121
139
168
196
20
40
60
80
100
120
140
160
180
200

FIG 11

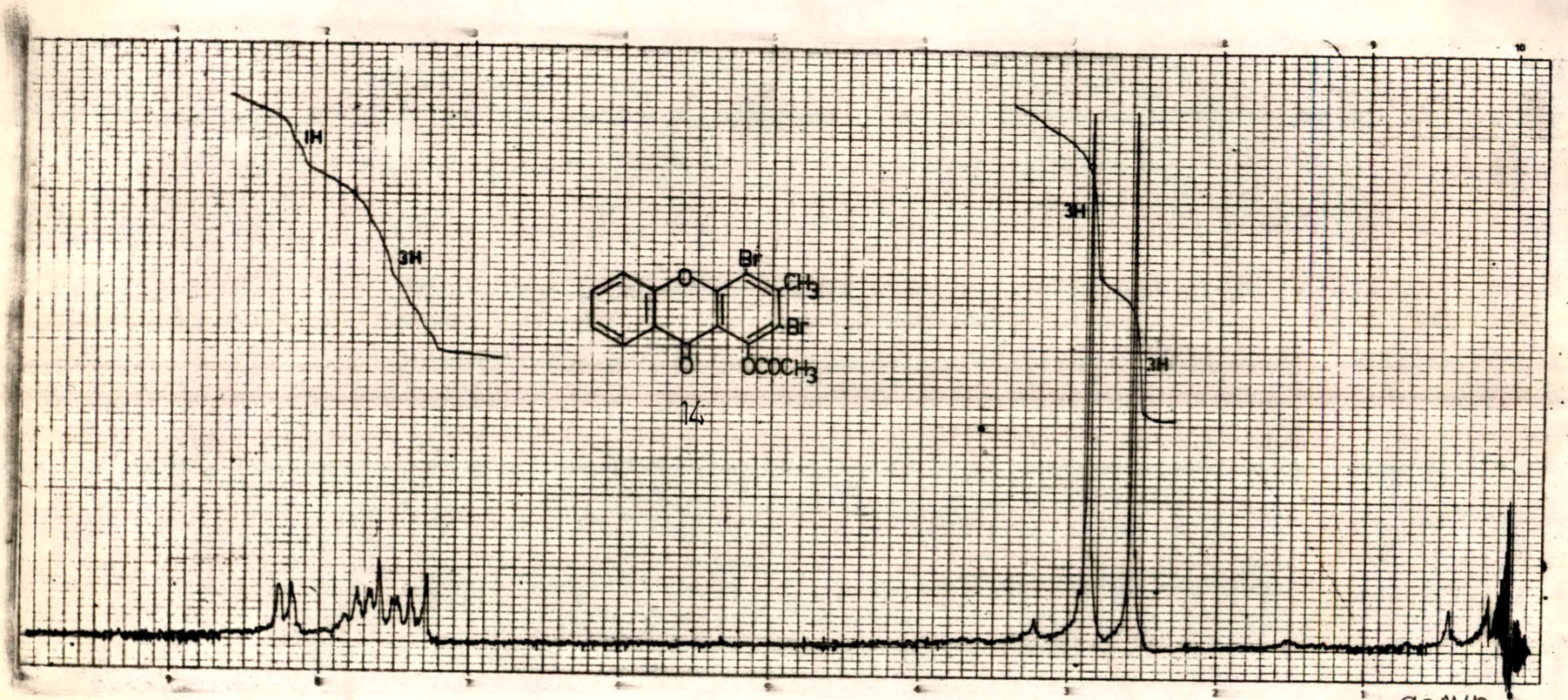
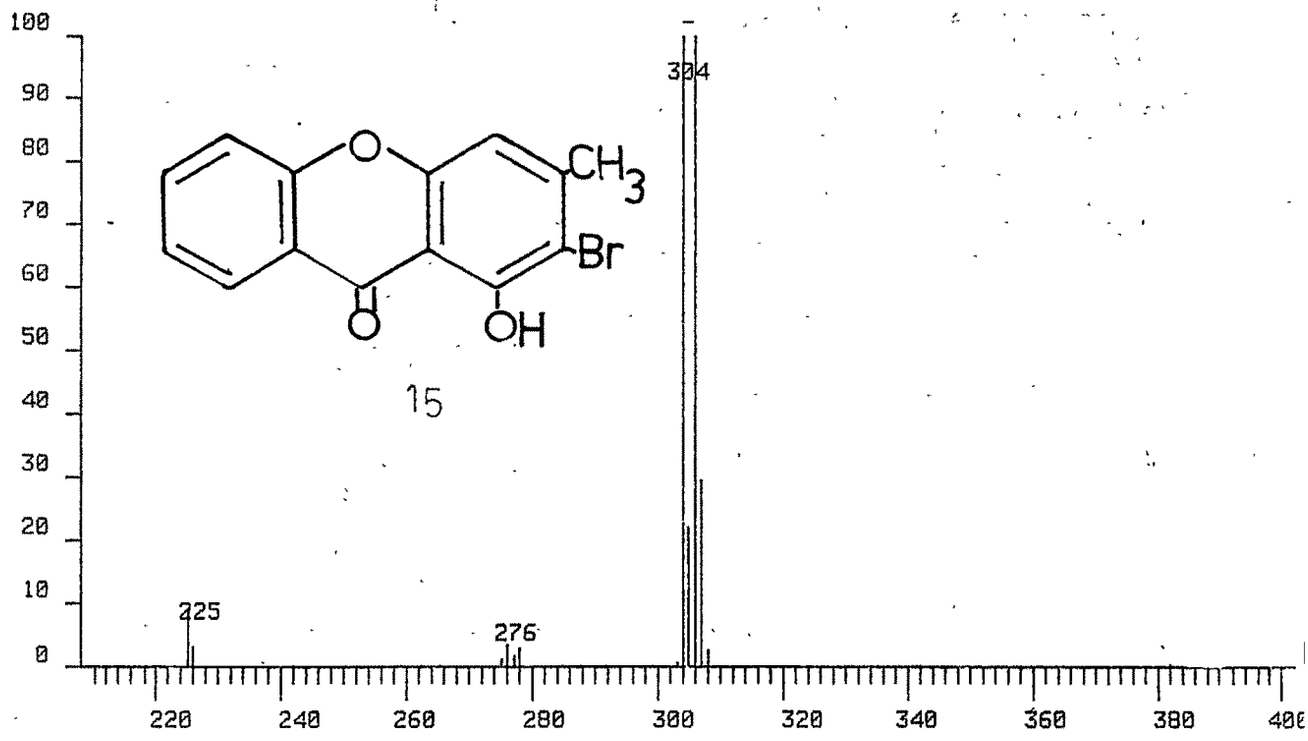


FIG 12


100
90
80
70
60
50
40
30
20
10
0
304
225
276
220
240
260
280
300
320
340
360
380
CH3
Br
OH
O

15

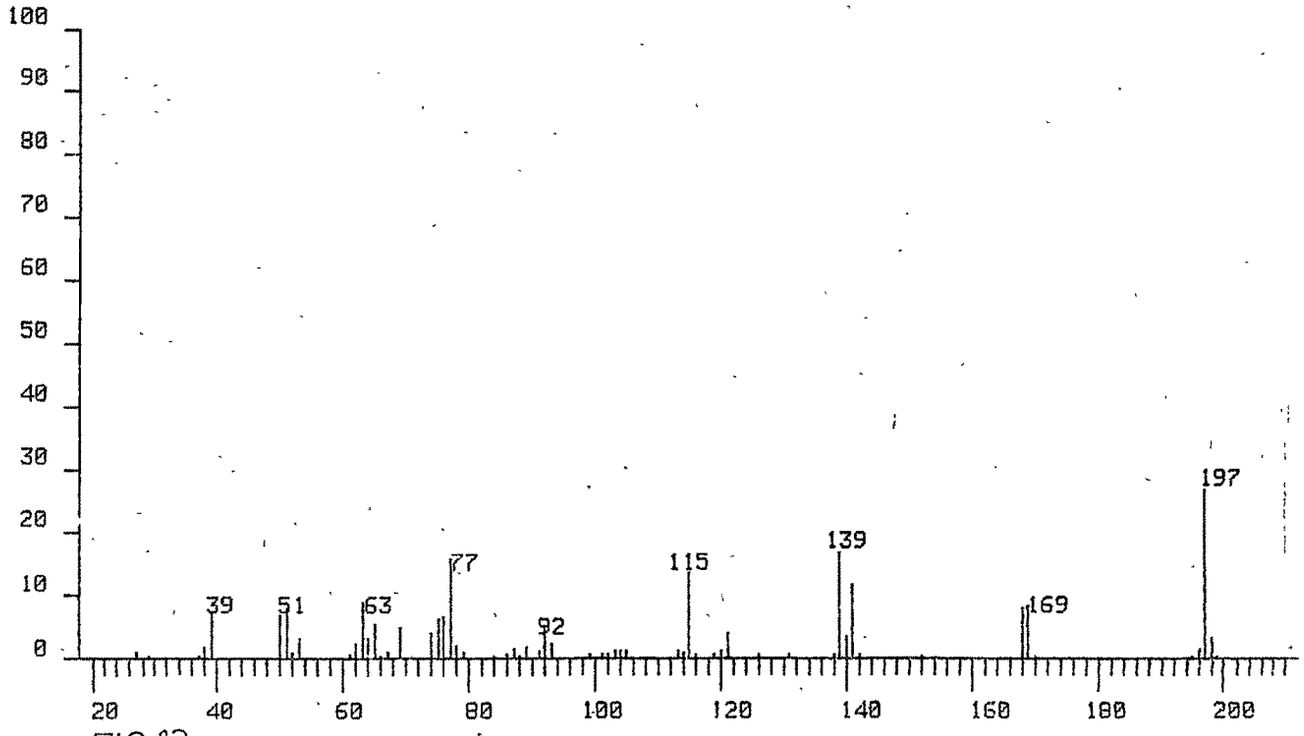

100
90
80
70
60
50
40
30
20
10
0
197
139
115
77
63
51
39
92
169
20
40
60
80
100
120
140
160
180
200

FIG 13

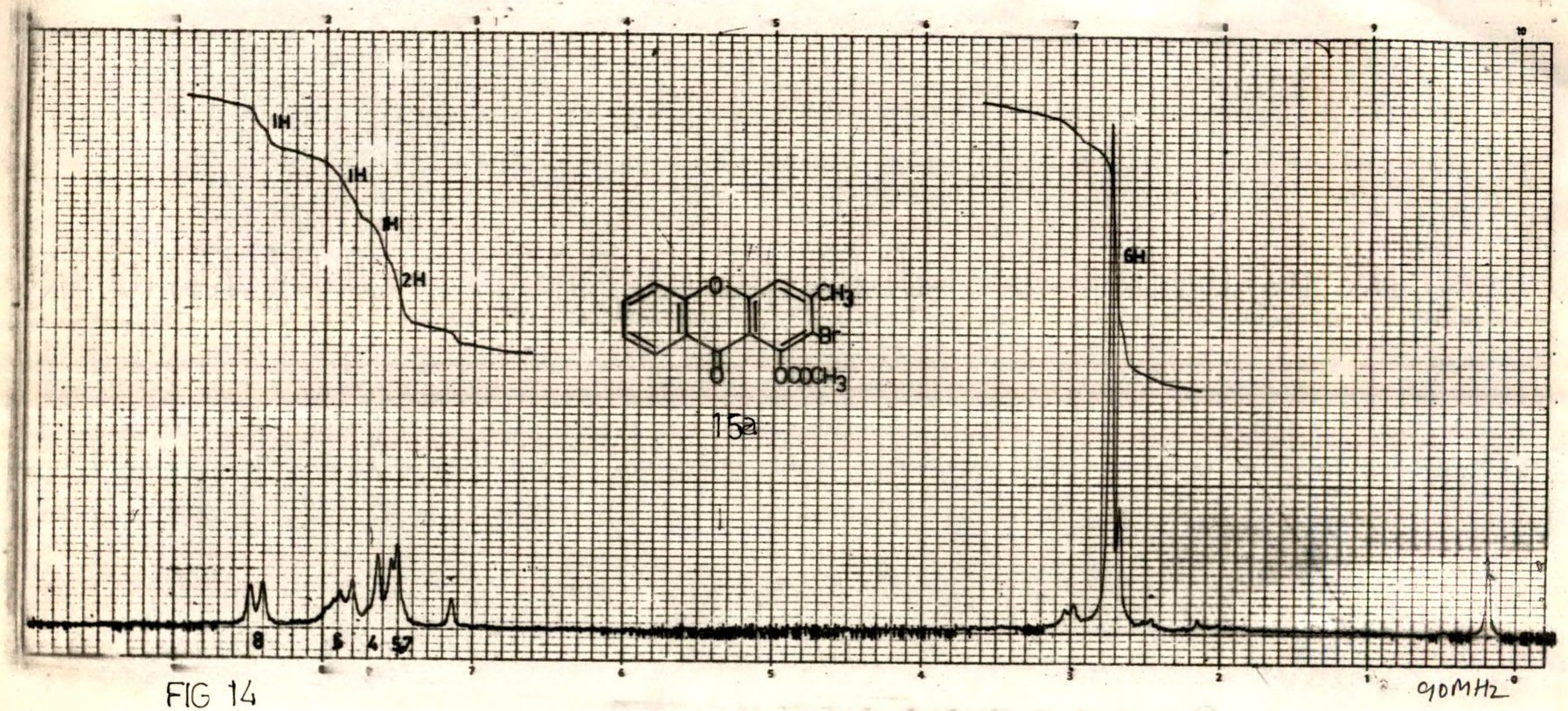
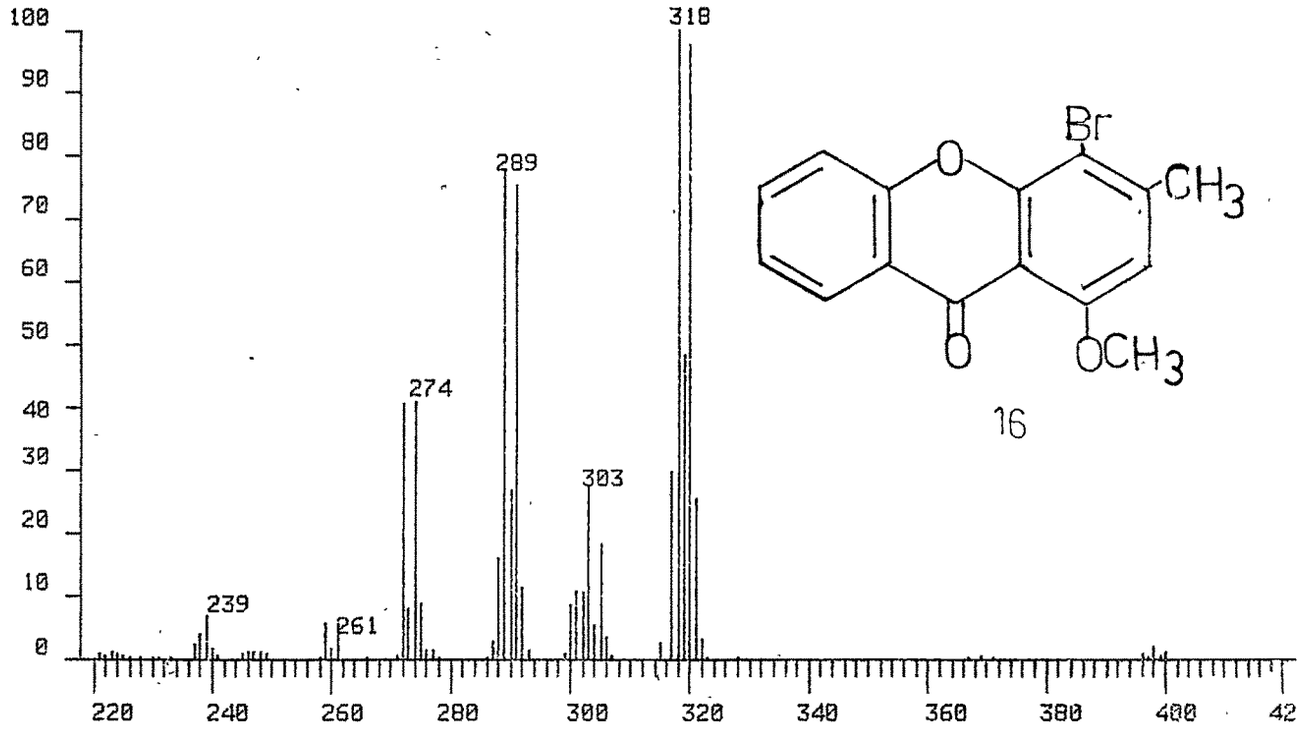


FIG 14


100
90
80
70
60
50
40
30
20
10
0
318
289
274
303
239
261
220
240
260
280
300
320
340
360
380
400
Br
O
CH3
O
OCH3

16

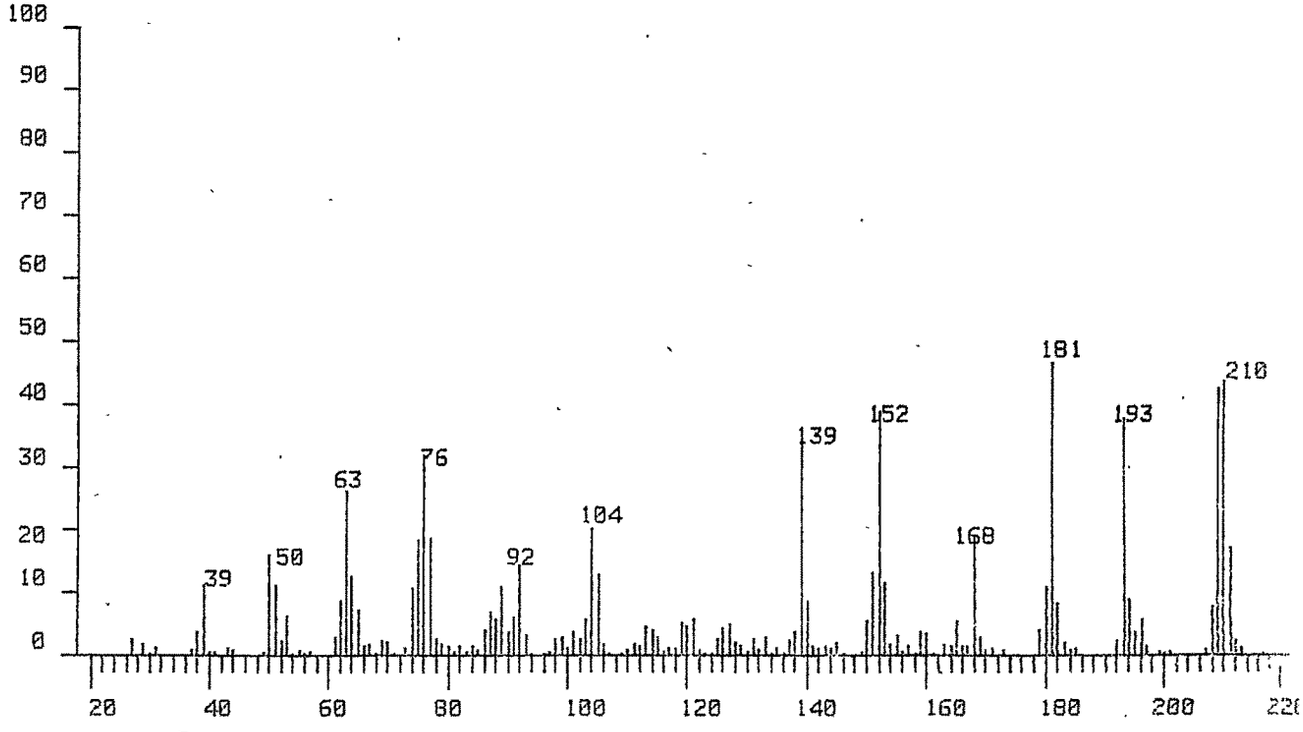

100
90
80
70
60
50
40
30
20
10
0
181
210
152
193
139
76
63
104
168
92
50
39
20
40
60
80
100
120
140
160
180
200

FIG 15

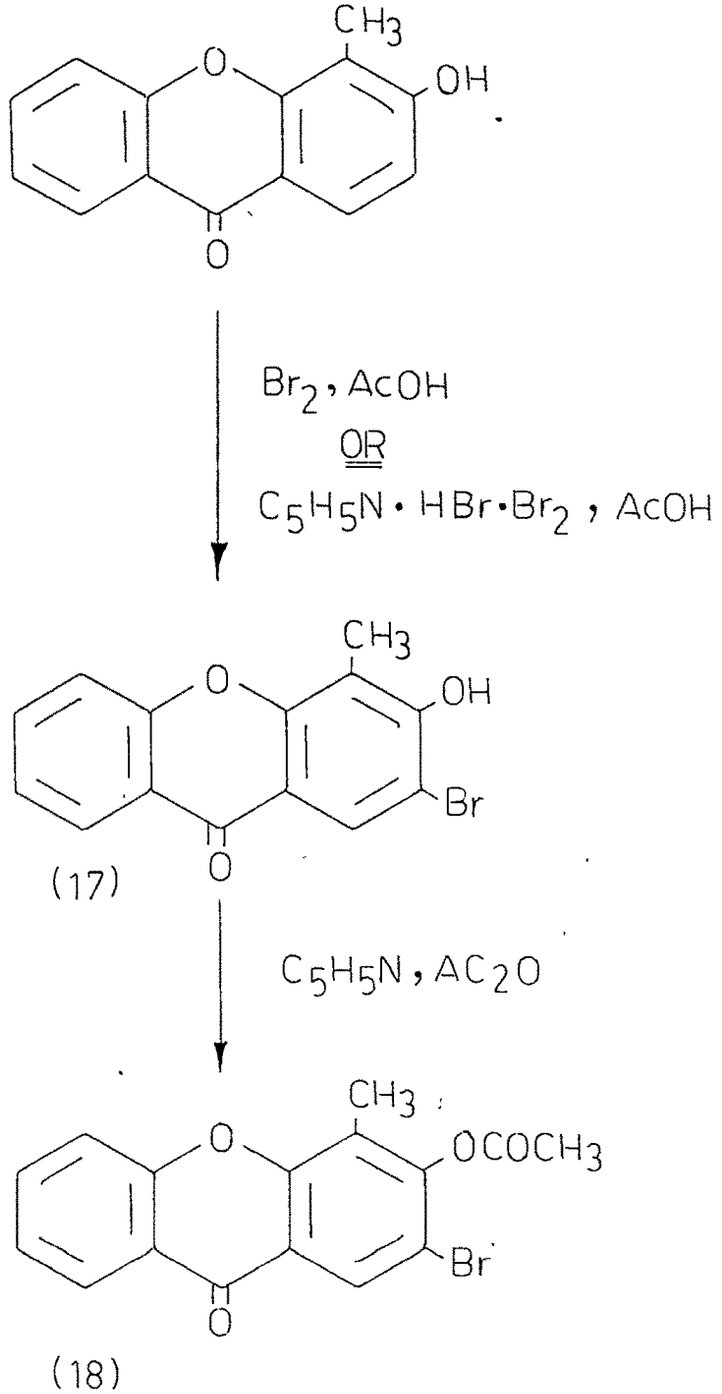
Bromination of 3-hydroxy-4-methylxanthone

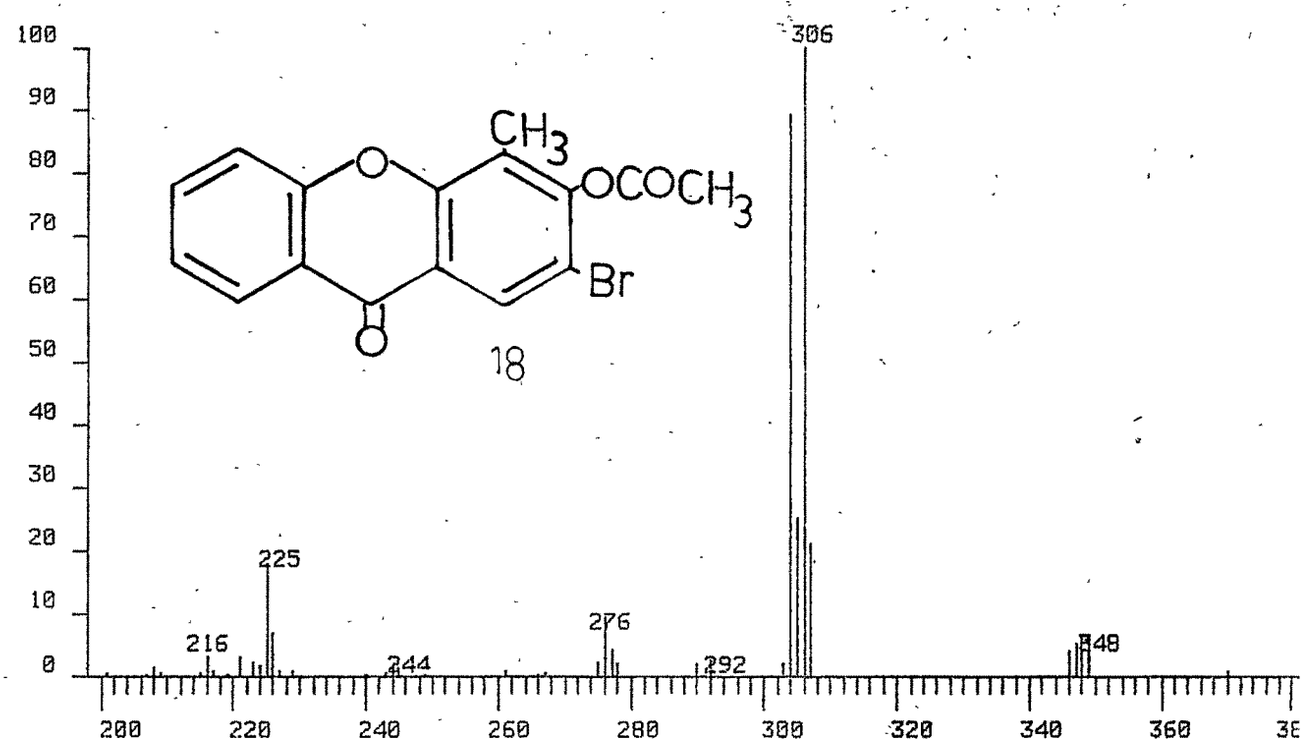
3-Hydroxy-4-methylxanthone gave 3-hydroxy-2-bromo-4-methylxanthone (17) with pyridine hydrobromide perbromide or bromine in acetic acid. The structure of (17) was established on the basis of Mass and NMR spectrum of its acetoxy derivative (18). Mass (Fig.16) m/e 348, 346, (5,6) NMR ($CDCl_3$) showed a highly down field singlet at δ 8.45 which is attributed to periproton at position 1 as it is affected by carbonyl group of xanthone and bromine at position 2, the down field double doublet at δ 8.3 is due to another periproton at position 8, 7.75, td, J=8,8,2Hz, H-6, 7.75 to 7.35, multiplet, 2H, H-5 and H-7, 2.45 overlap singlet for the six protons due to the methyl group at position 4 and $OCOCH_3$ group at position 3.

Synthesis of 7-bromo-1-hydroxyxanthone (19) and 7-bromo-3-hydroxyxanthone (20)

Condensation of methyl 5-bromo-salicylate with resorcinol

A mixture of resorcinol and methyl 5-bromo-salicylate was refluxed in diphenyl ether for 18 hr. The pasty mass, obtained after steam distillation, was passed through a silica gel coloumn and eluted with petroleum ether to give 7-bromo-1-hydroxyxanthone (19), the structure of which was


CH3
O
OH
O
Br2, AcOH
OR
C5H5N · HBr·Br2 , AcOH
CH3
O
OH
Br
O
(17)
C5H5N, AC2O
CH3
O
OCOCH3
Br
O
(18)


100
90
80
70
60
50
40
30
20
10
0
306
225
216
244
276
292
348
200
220
240
260
280
300
320
340
360
CH3
OCOCH3
Br
O
18

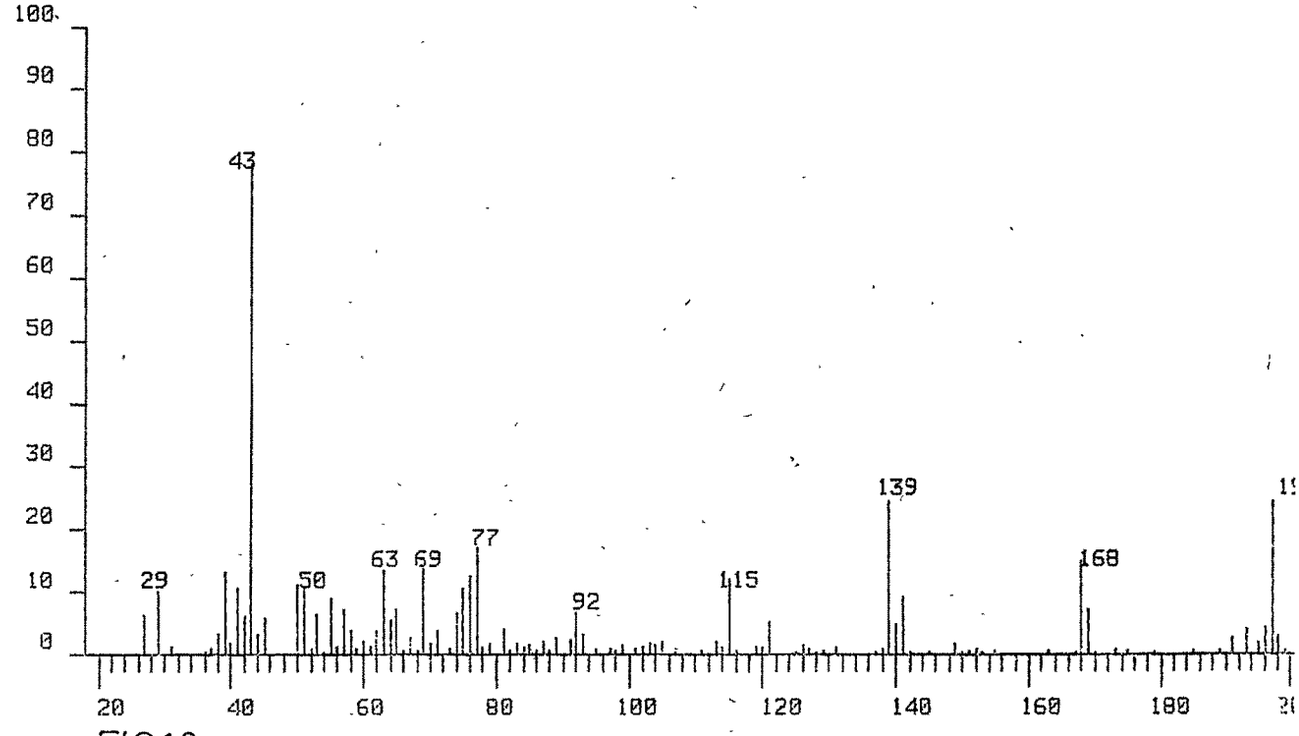

100
90
80
70
60
50
40
30
20
10
0
43
29
50
63
69
77
92
115
139
168
20
40
60
80
100
120
140
160
180

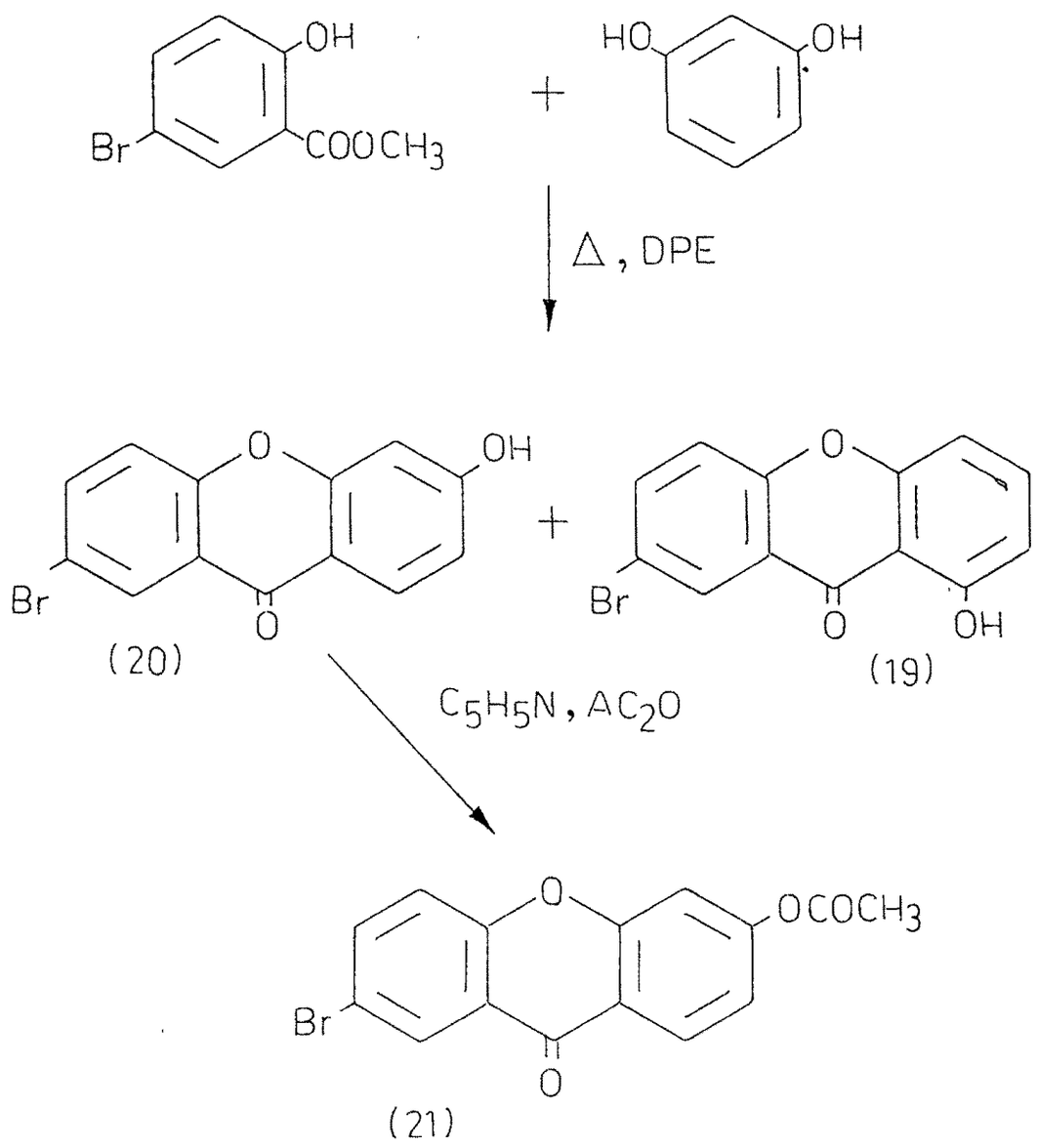
FIG16

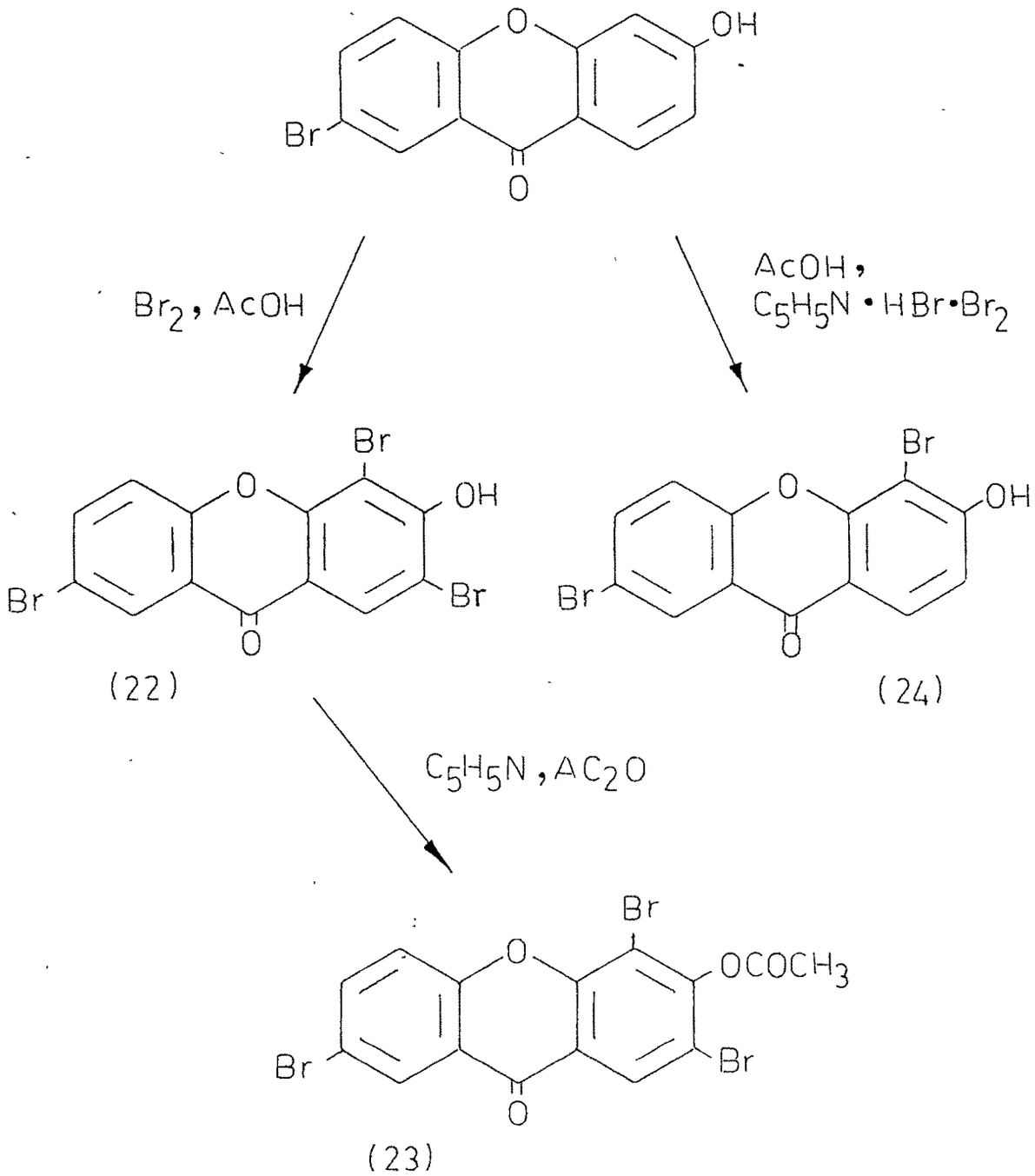
assigned on the basis of its NMR and Mass spectral data, mass (Fig.17) m/e 334, 332 suggest the presence of one bromine in the product. In the NMR (CCl_4) a doublet is observed at δ 8.4 having coupling constant of 2Hz (meta coupling) and is attributed to the proton at position 8. Position one is occupied by the -OH group, signal of which appears at δ 12.3; 7.6 to 7.2, multiplet, 3H, H-2, H-4 and H-5; 7.8, double doublet, 1H, J=9,2Hz, H-6; 6.8, td, J=8, 8, 1.5Hz, H-3. Elution with benzene-chloroform and chloroform - methanol 95:5 gave a product, which was characterized as 7-bromo-3-hydroxyxanthone (20) on the basis of mass and NMR spectrum of its acetoxy derivative (21). Mass (Fig.18) m/e 332, 330, 292, 290 (100) NMR ($CDCl_3$) δ 8.4, doublet, J=1.5Hz, (meta coupling) so it must be due to the periproton at position 8; 8.3, doublet, 1H, J=9Hz (orthocoupling), proton at position 1; 7.78, dd, 1H, J=9,2Hz, proton at position 6; 7.37, doublet, 1H, J=9Hz, proton at position 5; 7.3, dd, 1H, J=9,2Hz, proton at position 4; 7.13, dd, 1H, J=9,2Hz, proton at position H-2; 2.35, s, 3H, $OCOCH_3$.

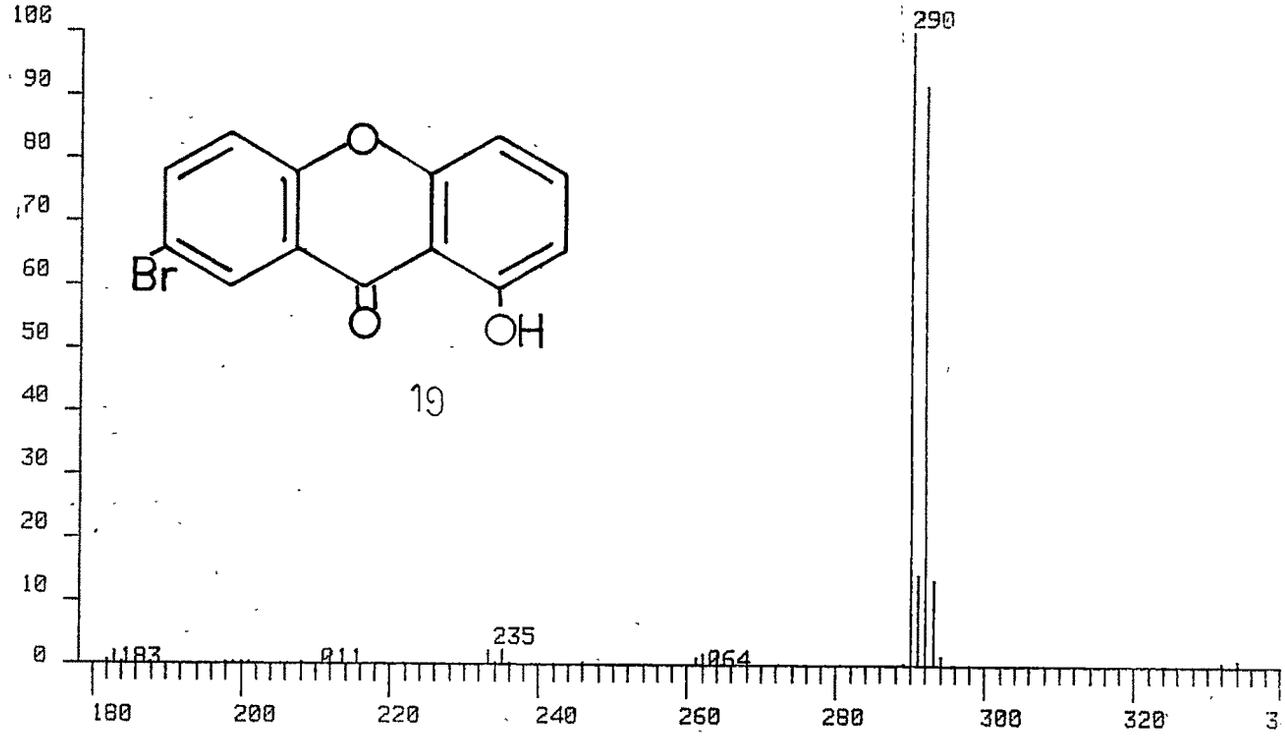
Bromination of 7-bromo-3-hydroxyxanthone

Bromination of 7-bromo-3-hydroxyxanthone with bromine in acetic acid gave 2,4,7-tribromo-3-hydroxy xanthone (22) structure of which was confirmed by NMR

and mass spectra of its acetoxy derivative (23). mass (Fig.19) m/e 494, 492, 490, 488 intensity ratio of molecular ion peak, 1:3:3:1, suggest that it is a tribromo compound hence it is concluded that dibromination has taken place, NMR ($CDCl_3$) (Fig.20) showed two peaks in highly down field aromatic region one singlet at δ 8.51, which is due to the periproton at position 1; presence of bromine at position 2 shifts the peaks of the proton H-2 towards the down field, 8.4, doublet of J value 2Hz which is attributed to the periproton at position 8; 7.85, dd, 1H, J=9 2Hz, proton at position 6; 7.48 doublet of J=9Hz proton at position 5; and 2.45, singlet, 3H, $OCOCH_3$. Bromination of 7-bromo-3-hydroxyxanthone with pyridine hydrobromide perbromide in acetic acid at room temperature gave the dibromo compound (22) instead of monobromo derivative hence the bromination was carried out at low temperature. Compound (20) with pyridine hydrobromide perbromide in chloroform - methanol mixture gave 4,7-dibromo-3-hydroxyxanthone (24), the characterization of which was done on the basis of elemental analysis and its mass and NMR spectral studies. Mass (Fig.21) m/e 372, 370, 368 intensity pattern indicate that it is a dibromo derivative NMR ($CDCl_3$) (Fig.22,23) showed a doublet of small coupling constant 2Hz at δ 8.1 which could be assigned


OH
Br
COOCH3
HO
OH
Δ, DPE
O
OH
Br
O
(20)
O
Br
O
OH
(19)
C5H5N, AC2O
O
OCOCH3
Br
O
(21)


Br
O
OH
O
Br_2, AcOH
AcOH,
$C_5H_5N \cdot HBr \cdot Br_2$
Br
O
OH
Br
Br
O
(22)
Br
O
OH
Br
O
(24)
C_5H_5N, AC_2O
Br
O
$OCOCH_3$
Br
Br
O
(23)


100
90
80
70
60
50
40
30
20
10
0
290
235
183
211
264
180
200
220
240
260
280
300
320
Br
OH

19

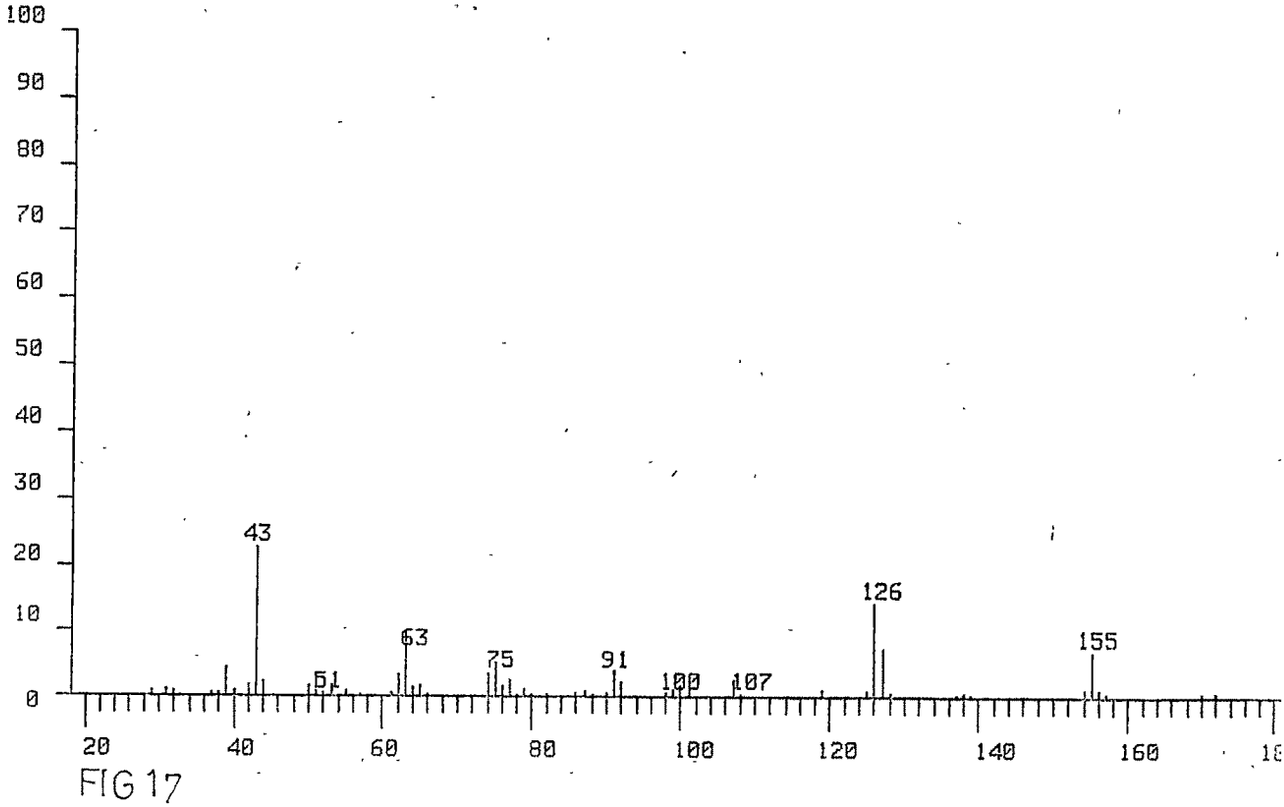
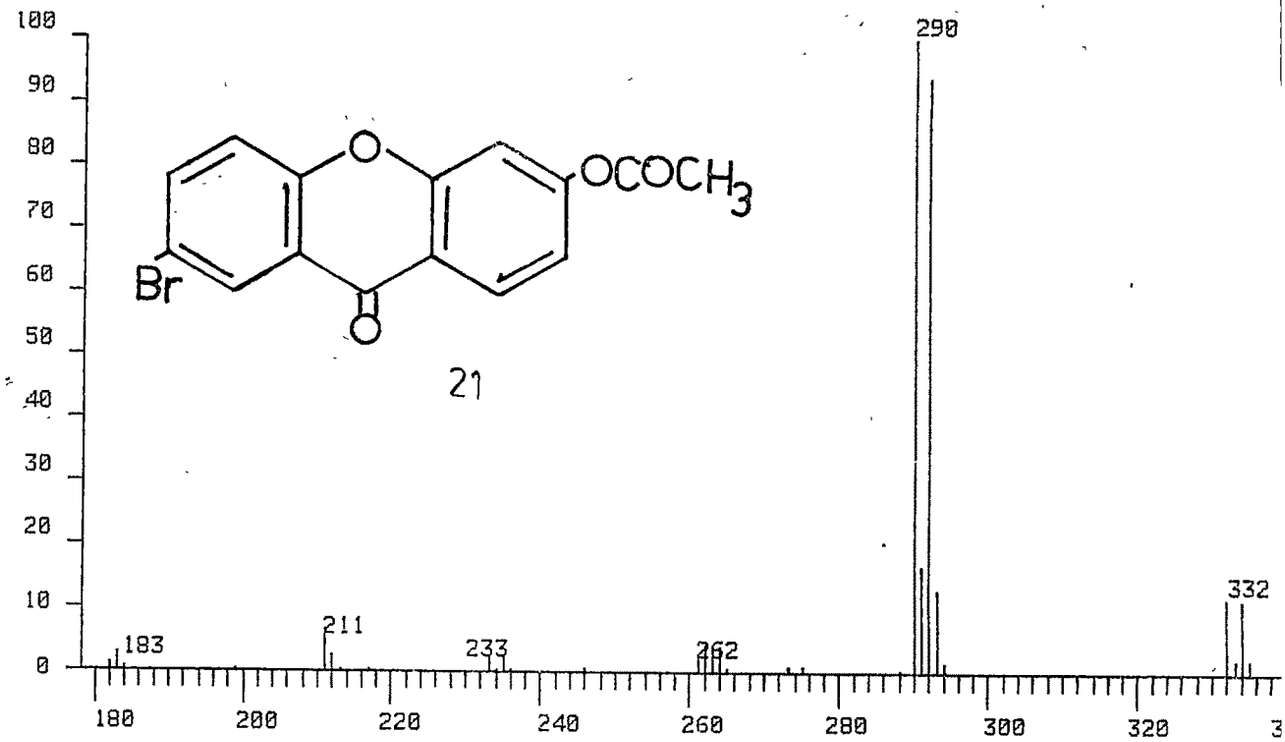

100
90
80
70
60
50
40
30
20
10
0
43
63
51
75
91
100
107
126
155
20
40
60
80
100
120
140
160

FIG 17


100
90
80
70
60
50
40
30
20
10
0
290
332
183
211
233
262
180
200
220
240
260
280
300
320
OCOCH3
Br
O
O

21

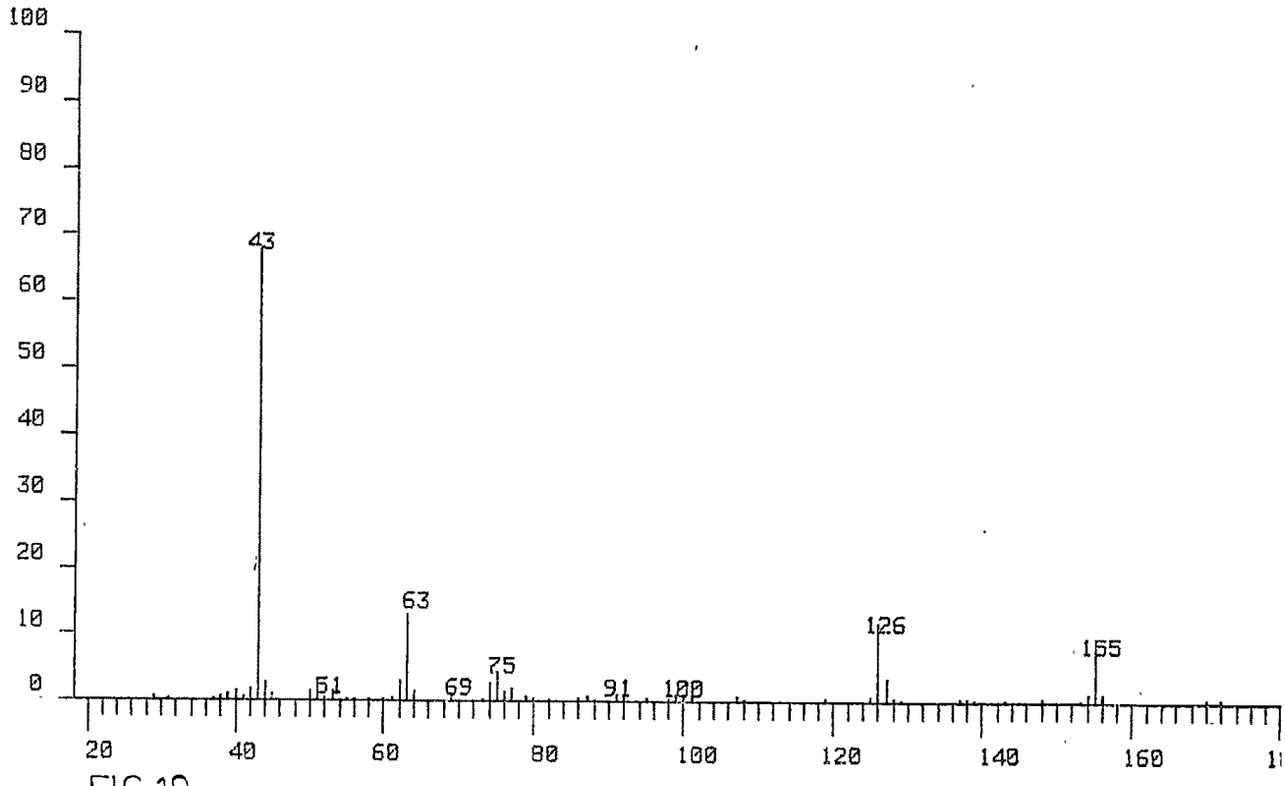

100
90
80
70
60
50
40
30
20
10
0
43
63
126
155
51
69
75
91
100
20
40
60
80
100
120
140
160

FIG 18

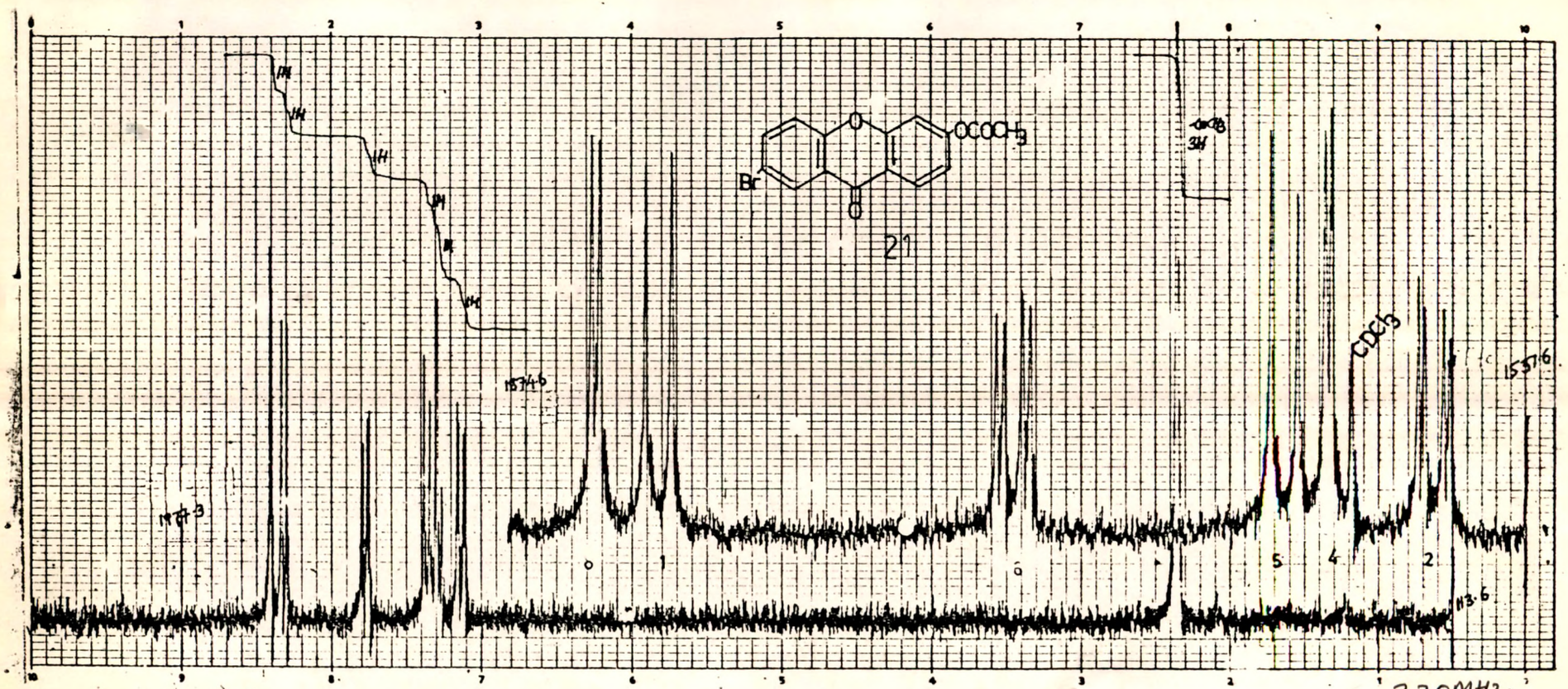
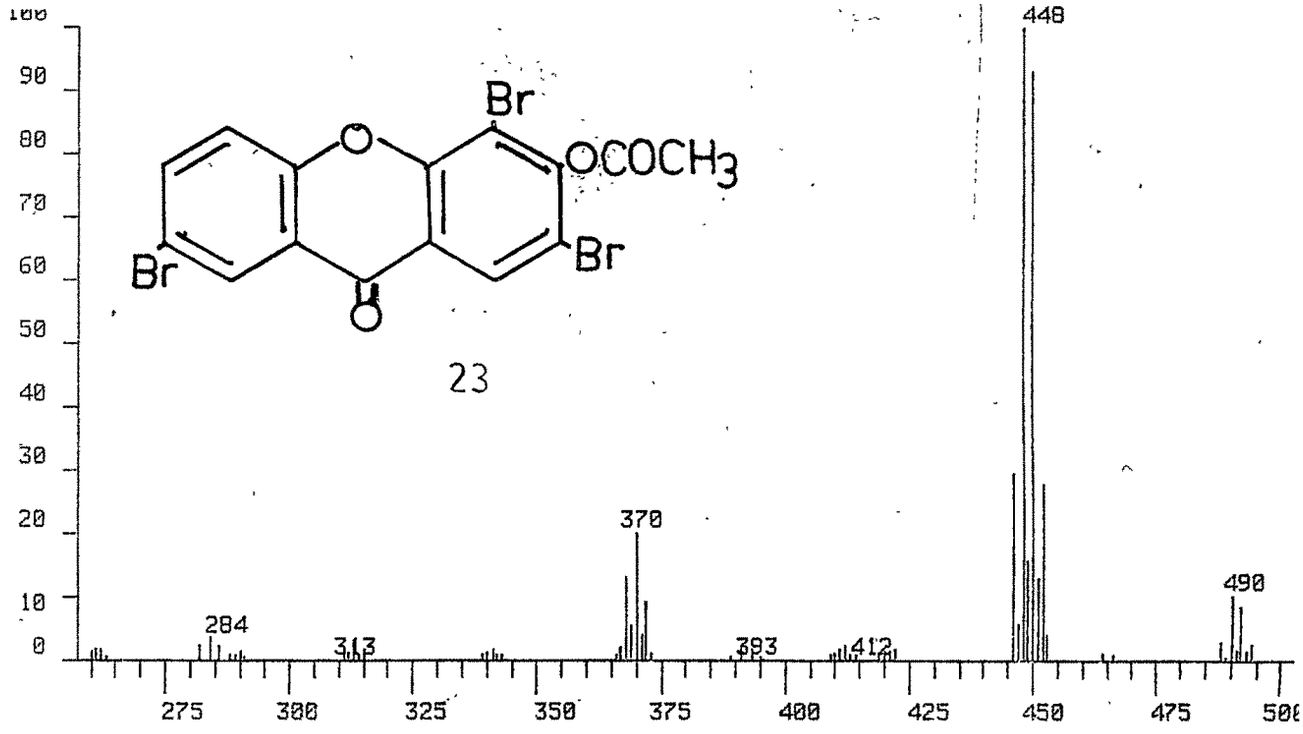


FIG 18a


Br
OCOCH3
Br
Br
O
O

23

100
90
80
70
60
50
40
30
20
10
0
448
370
490
284
313
393
412
275
300
325
350
375
400
425
450
475
500

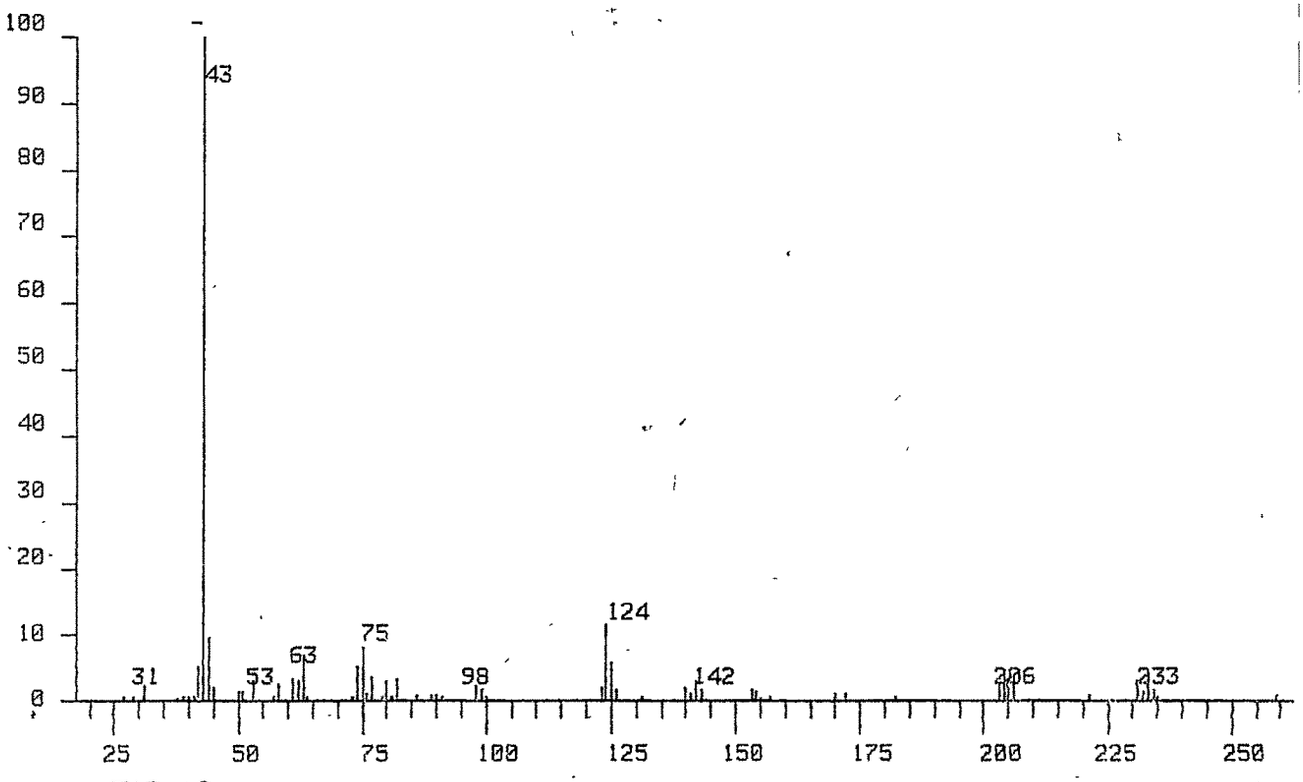

100
90
80
70
60
50
40
30
20
10
0
43
124
75
63
31
53
98
142
206
233
25
50
75
100
125
150
175
200
225
250

FIG 19

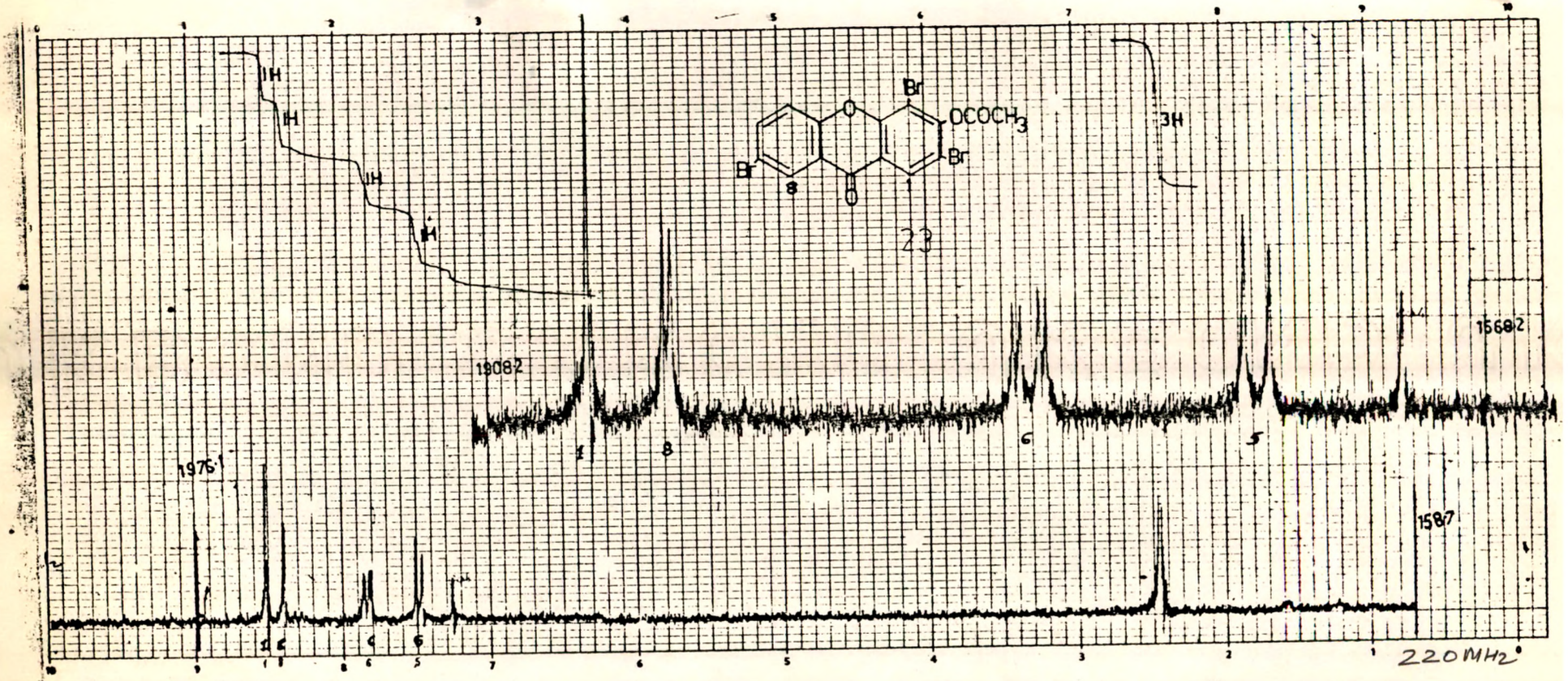
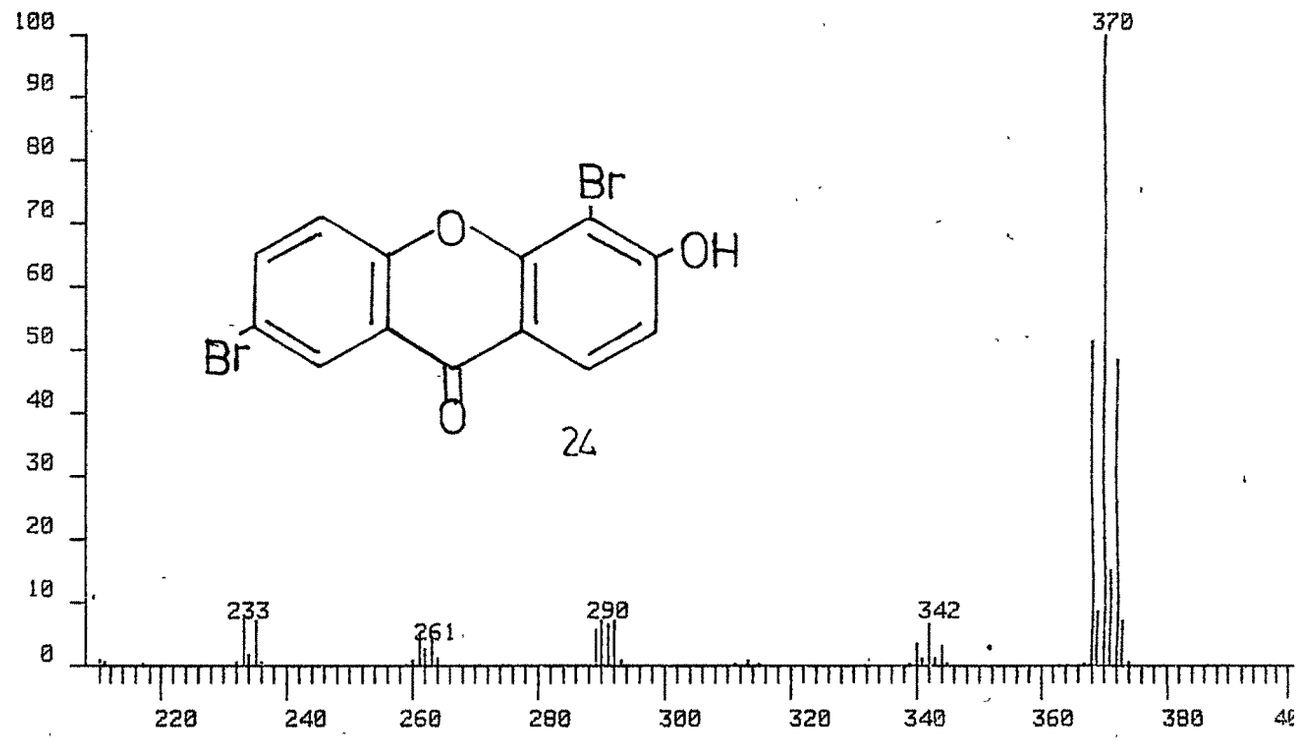

1H
1H
1H
1H
3H
Br
OCOCH3
Br
Br
O
O
8
1
23
1908.2
1976.1
1568.2
1587
8
6
5
220MHz

FIG 20


Br
OH
O
Br
O
24
100
90
80
70
60
50
40
30
20
10
0
370
233
261
290
342
220
240
260
280
300
320
340
360
380

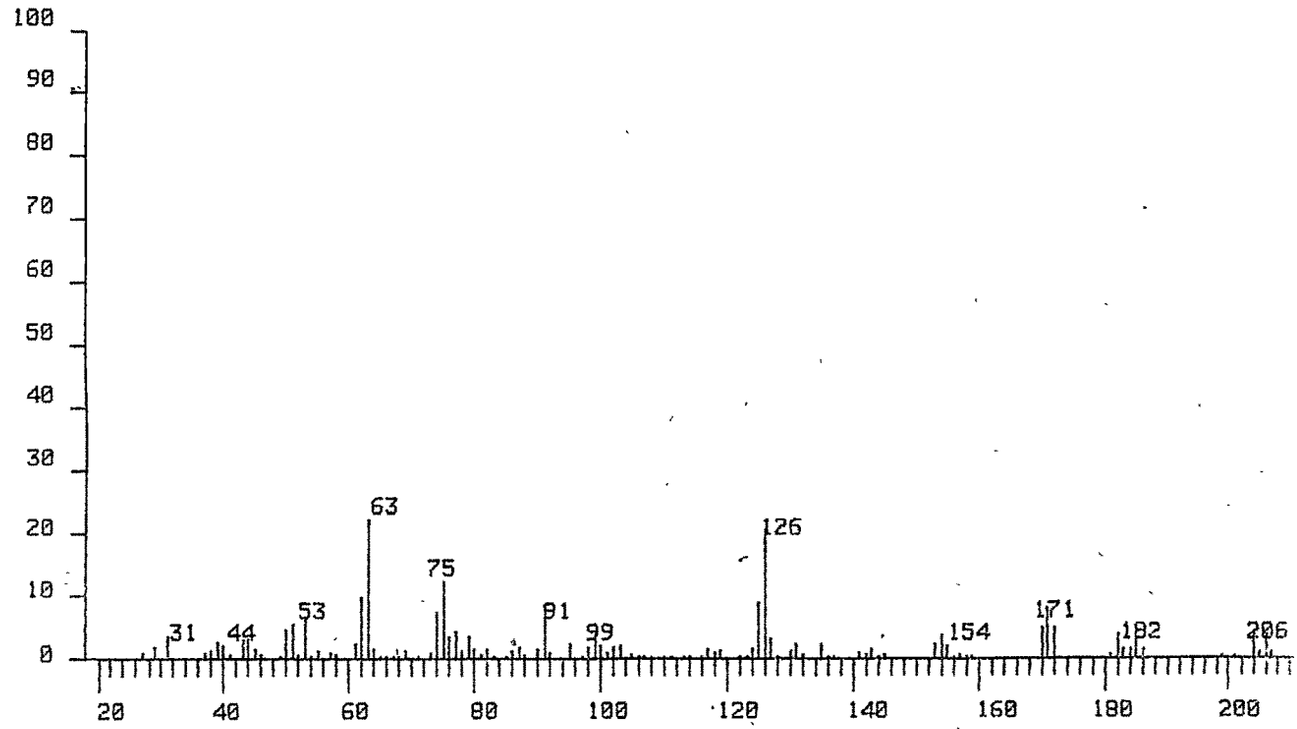

100
90
80
70
60
50
40
30
20
10
0
63
126
75
31
44
53
91
99
154
171
182
206
20
40
60
80
100
120
140
160
180
200

FIG 21

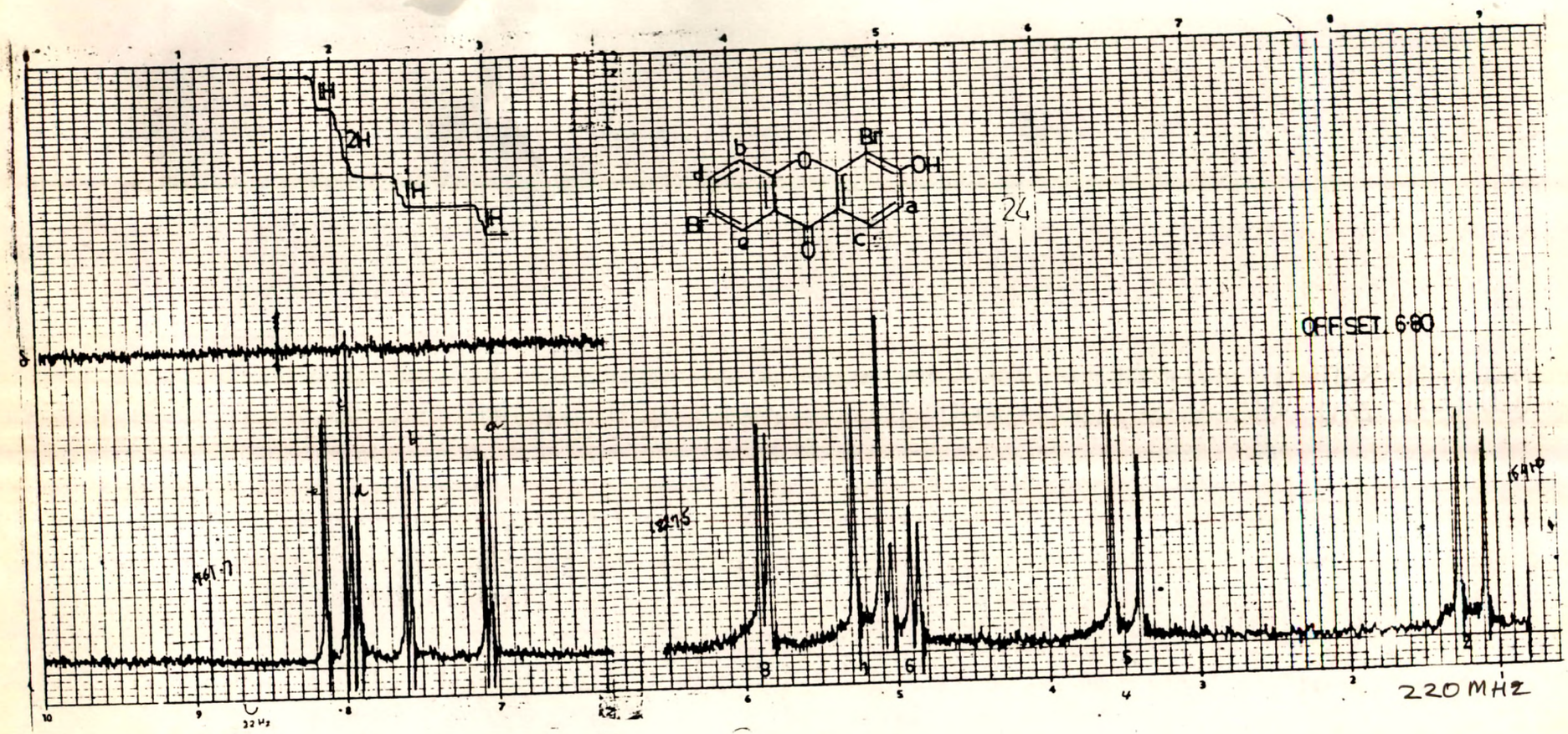


FIG 22

to the proton at position 8; δ 7.99, doublet, J=9Hz, for proton at position-1; 7.92, dd, 1H, J=9, 2Hz, proton at position 6; 7.58, doublet, J=9Hz, proton at position 5; 7.07, doublet, 1H, J=9Hz, proton at position 2; This confirms the assigned structure (24).

The electronic impact induced fragmentation of xanthone has been reported[30] and the influence of hydroxy and methoxy substituents on the fragmentation patterns has been studied in detail[31]. The mass spectra of halogenated xanthones have been reported[32], but no attempts have so far been made to study the mass spectra of bromo hydroxyxanthones. Mass spectrometry of 2-bromo-1-hydroxy-, 7-bromo-1-hydroxy-,2-bromo-1-hydroxy-3-methyl-, 3-acetoxy-4-bromo-, 2-acetoxy-1-bromo-, 3-acetoxy-7-bromo-, 3-acetoxy-2-bromo-4-methyl-, 2,4-dibromo-1-hydroxy-, 2-acetoxy-1, 4-dibromo-, 3-acetoxy-2, 4-dibromo-, 2,4-bromo-3-methyl-1-hydroxy-, and 3-acetoxy-2,4,7-tribromo xanthones has been presented.

Monobromohydroxyxanthones

The characteristic fragmentation of hydroxyxanthones[31] is the ready loss of CO which is followed by a loss of CHO. In case of bromohydroxyxanthones, the molecular ion is the base peak. The major fragmentation route (Scheme 1) is initiated by the loss of Br followed by the successive loss

of two molecules of CO leading to the ion of m/e 183, which then follow the usual fragmentation of xanthone[31]. In case of 2-bromo-1-hydroxy-3-methylxanthone, no loss of OH or Me is observed which may be due to the formation of stable ion, like structure of xanthone (Scheme 2). In case of 2-bromo-1-hydroxyxanthone and 7-bromo-1-hydroxy xanthone, absence of (M^+ —— OH) and M^+——Br——OH) peaks indicates that the alternate path of fragmentation[2] is not possible in these bromohydroxyxanthones.

Acetoxybromoxanthones

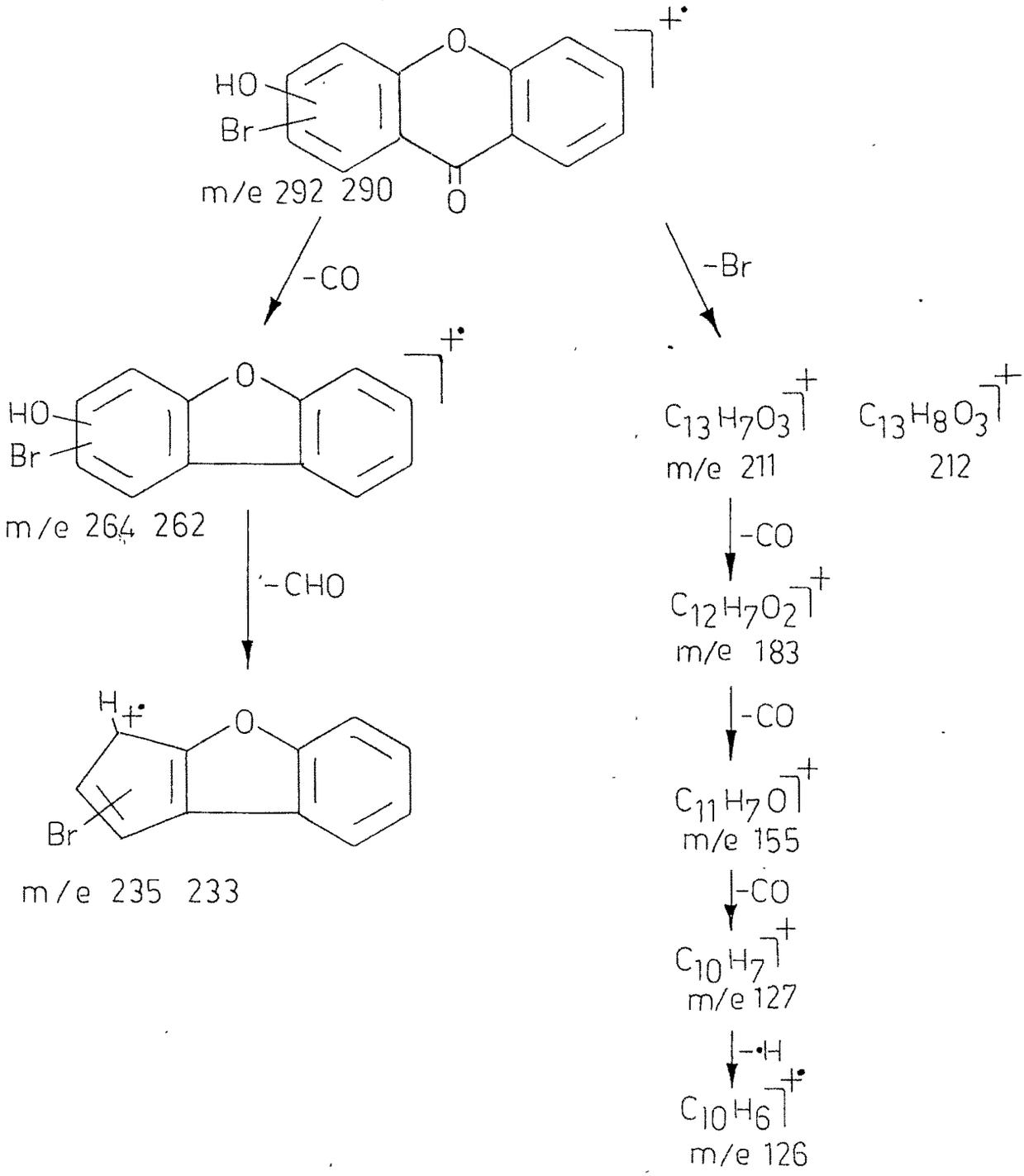
The mass spectra of 3-acetoxy-4-bromoxanthone, 3-acetoxy-7-bromoxanthone, 2-acetoxy-1-bromoxanthone, and 3-acetoxy-2-bromo-4-methylxanthone show the characteristic loss of $-COCH_2$ group by McLafferety rearrangement from the molecular ion to form the stable bromohydroxyxanthone ion radical which forms the base peak m/e 292, 290 (100%) in the spectrum and not the parent ion peak. The characteristic loss of CO from xanthone nucleus results after the loss of $-COCH_2$. Loss of Br is then observed from the base peak, which gives m/e 212 (3-10%) and further fragmentation then proceeds according to fragmentation pattern of monohydroxyxanthones (Scheme 1). Another way of fragmentation from the base peak m/e 290, 292 is the loss of CO followed by the loss of CHO.

Dibromoxanthones

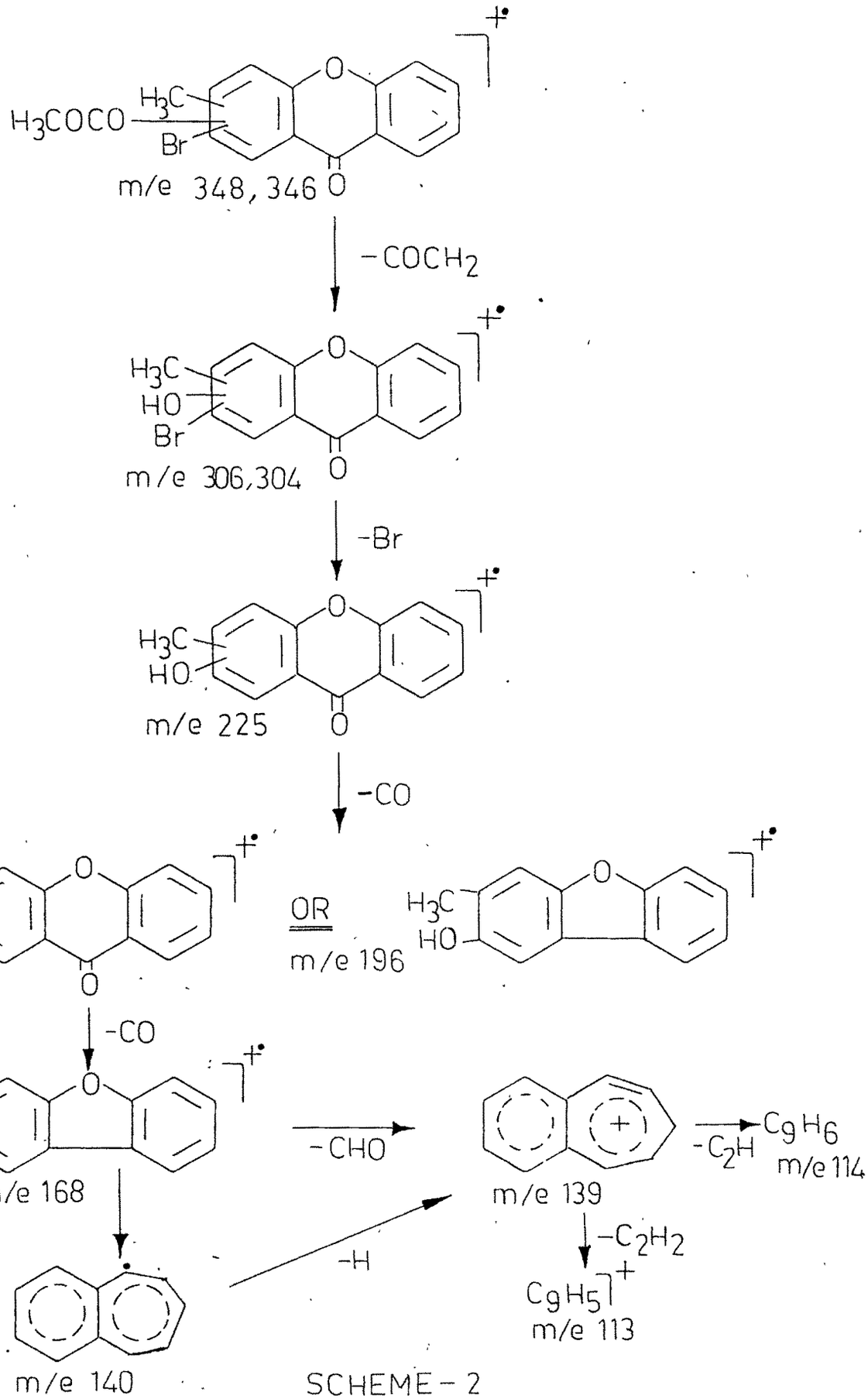
In the mass spectrum of 2,4-dibromo-1-hydroxyxanthone, molecular ion m/e 370 (100%) is the peak from which the loss of CO is observed. However, the actual fragmentation starts after the loss of one -Br from the base peak and then the fragmentation pattern is similar to that of monobromohydroxyxanthones. In case of 2-acetoxy-1,3-dibromoxanthone, molecular ion peak m/e 370 (27%) is not the base peak, first loss of $-COCH_2$ and Br occurs to give the base peak at m/e 290 (100%). In case of 3-acetoxy-2,4-dibromoxanthone, the base peak is observed at m/e 368, 370, 372 (52, 100, 50) after the loss of $COCH_2$. In case of 1-hydroxy-2-bromo-3-methylxanthone, molecular ion is the base peak.

Tribromoacetoxyxanthone

After the loss of $-COCH_2$, base peak is obtained at m/e 446, 448, 450, 452 (33%, 100%, 93%, 28%) indicating the presence of three bromines in the molecule. After the loss of $-COCH_2$ and Br molecule, fragmentation pattern remains same as that of dibromohydroxyxanthones (Scheme 2). The decomposition of the isomaric monobromohydroxyxanthones under electron impact are very similar to each other so that it is difficult to distinguish between them in this way but it is easy to know that how many bromine atoms are present in the molecule by looking at the base peak pattern or molecular ion peak.


HO
Br
m/e 292 290
-CO
-Br
HO
Br
m/e 264 262
-CHO
Br
m/e 235 233
$C_{13}H_7O_3^+$
m/e 211
$C_{13}H_8O_3^+$
212
-CO
$C_{12}H_7O_2^+$
m/e 183
-CO
$C_{11}H_7O^+$
m/e 155
-CO
$C_{10}H_7^+$
m/e 127
-•H
$C_{10}H_6^{+\bullet}$
m/e 126

SCHEME-1


H3COCO
H3C
Br
O
m/e 348, 346
-COCH2
H3C
HO
Br
m/e 306,304
-Br
H3C
HO
m/e 225
-CO
OR
m/e 196
H3C
HO
-CO
m/e 168
-CHO
m/e 139
-C2H
C9H6
m/e 114
-C2H2
C9H5
m/e 113
-H
m/e 140

SCHEME – 2

EXPERIMENTAL

For general remarks, see Chapter II, Experimental.

2,4-Dibromo-3-hydroxyxanthone (1)

3-Hydroxyxanthone (4.2 g; 0.02 mol) was dissolved in glacial acetic acid (100 ml) and to this liquid bromine (2 ml) was added. The reaction mixture was stirred for 2 hr and poured into water. The separated product was crystallised from dimethyl formide to give (1) as yellow needles m.p. 282° (lit.,[27] m.p. 279°) Yield (3.0 g).

Analysis : Found : C, 42.75; H, 2.280 %.

$C_{13}H_6O_3Br_2$: requires : C, 42.39; H, 1.902 %.

2,4-Dibromo-3-acetoxyxanthone (2)

The compound (1) (0.5 g) acetic anhydride (5 ml) and pyridine (1 ml) was heated on a water bath for 12 hr. The reaction mixture was worked up as before gave the product which crystallised from chloroform or acetic acid or alcohol to give (2) as white needles m.p. 222° Yield 0.3 g.

Analysis : Found : C, 43.88; H, 2.28 %.

$C_{15}H_8O_3Br_2$: requires : C, 43.49; H, 1.942 %.

3-Hydroxy-4-bromoxanthone (3)

3-Hydroxyxanthone (2.0 g, 0.01 mol) was dissolved in glacial acetic acid (80 ml) and warmed upto 55°C. Pyridine

hydrobromide perbromide (3.2 g., 0.01 mol) was then added. The reaction mixture was stirred for 30 min. and diluted with water, the product obtained was crystallised from ethyl acetate to give (3) as brown needles, m.p. 254° (1.8 g).

Analysis : Found : C, 53.33; H, 2.545 %.

$C_{13}H_7O_3Br$: requires : C, 53.79; H, 2.41 %.

3-Acetoxy-4-bromoxanthone (4)

A mixture of product (3) (0.2 g) acetic anhydride (4 ml) and pyridine (1 ml) was heated on a water bath for 15 hr. The reaction mixture was worked up in usual manner. The product obtained was crystallised from alcohol gave (4) as yellowish white needles m.p. 181° (0.15 g).

Analysis : Found : C, 54.24; H, 2.91 %.

$C_{15}H_9O_4Br$: requires : C, 54.05; H, 2.70 %.

2-Bromo-3-hydroxyxanthone (5)

2,4-Dibromo-3-hydroxyxanthone (2) (2.35 g) was refluxed with dimethylaniline for 1/2 hr. The reaction mixture was then poured into cold dil.hydrochloric acid, the separated product was filtered off and crystallised from alcohol-benzene mixture to yield (5) as white needles m.p. 310° yield 40 to 50 %.

2,4-Dibromo-1-hydroxyxanthone (6)

1-Hydroxyxanthone (2.1 g., 0.01 mol) was dissolved in glacial acetic acid (50 ml) and to this liquid bromine (1 ml) was added. The reaction mixture was stirred for 3 hr and worked up as described earlier. The product obtained was crystallised from benzene gave (6) as yellow shining pellets m.p. 228° (lit[27]; 226°). Yield (1.6 g).

Analysis : Found : C, 42.78; H, 2.333 %.

$C_{13}H_6O_3Br$: requires : C, 42.39; H, 1.90 %.

NMR ($CDCl_3$) : δ 13.52, s, 1H, OH; 7.85 to 7.3, m, 3H, H-5, H-6 and H-7; 8.15, s, 1H, H-3; 8.3, dd, 1H, J=9,2Hz, H-8.

2,4-Dibromo-1-acetoxyxanthone (7)

A mixture of compound (6) (0.2 g), acetic anhydride (5 ml) and pyridine (2 ml) was heated on a water bath for 20 hr. The reaction mixture was worked up as described before. The product obtained was crystallised from a mixture of benzene and petroleum ether gave (7) as pale yellow cubes m.p. 139°C.

Analysis : Found : C, 44.02; H, 2.19 %.

$C_{15}H_8O_3Br_2$: requires : C, 43.49; H, 1.942 %.

2-Bromo-1-hydroxyxanthone (8)

1-Hydroxyxanthone (2.0g.,0.01 mol) was dissolved in glacial acetic acid (50 ml), pyridine hydrobromide

perbromide was then added and the reaction mixture was stirred for 1 hr at room temperature. The reaction mixture was worked up as usual. The product obtained was crystallised from benzene to give (8) as yellow tiny needles m.p. 170°-72° yield (1.4 g).

Analysis : Found : C, 54.20; H, 2.766 %.

$C_{13}H_7O_3Br$: requires : C, 53.79; H, 2.413 %.

1,3-Dibromo-2-hydroxyxanthone (9)

2-Hydroxyxanthone (2.1g,0.01 mol) was dissolved in glacial acetic acid (100 ml) and to this bromine in acetic acid (5.5 ml; 4.75% w/v) was added slowly. The reaction mixture was stirred for 1 hr at 55°. The separated solid was filtered off, which was found to be 2-hydroxyxanthone (0.2g). The filtrate was diluted with water. The separated product was crystallised from aqueous dioxan gave (9) as yellow needles m.p. 205-7° (lit[27]; 202°) Yield 1.2 g.

1,3-Dibromo-2-acetoxyxanthone (10)

A mixture of (9) (0.2g), acetic anhydride (5 ml) and pyridine (1 ml) was heated on a water bath for 10 hr. The product obtained after usual work up, crystallised from aqueous alcohol gave (10) as brown needles m.p.175°.

Analysis : Found : C, 43.19; H, 2.34 %.

$C_{15}H_8O_4Br_2$ requires : C, 43.49; H, 1.942 %.

1-Bromo-2-hydroxyxanthone (11)

2-Hydroxyxanthone (0.532 g; 0.015 mol) was dissolved in glacial acetic acid (60 ml), pyridine hydrobromide perbromide (0.8g), was then added in one lot, reaction mixture was stirred for 1/2 hr at 50°C and allowed to stand over night at room temperature. The reaction mixture was worked up as usual. The product thus obtained was crystallised from acetic acid gave (11) as yellow needles m.p. 220°C Yield (0.4 g).

Analysis : Found : C, 54.20; H, 2.590 %.

$C_{13}H_7O_3Br$ requires : C, 53.79; H, 2.413 %.

1-Bromo-2-acetoxyxanthone (12)

A mixture of compound (11) (0.3g), acetic anhydride (5 ml) and pyridine (1 ml) was heated on a water bath for 11 hr. The reaction mixture was worked up as usual. The product obtained was crystallised from alcohol gave (12) as white needles. m.p. 198° (0.2 g).

Analysis : Found : C, 54.33; H, 2.873 %.

$C_{15}H_9O_4Br$ requires : C, 54.05; H, 2.70 %.

2,4-Dibromo-1-hydroxy-3-methylxanthone (13)

1-Hydroxy-3-methylxanthone (2.0g, 0.01 mol) was dissolved in glacial acetic acid (80 ml) and to this bromine in acetic acid (5.5 ml; 4.75 % w/v) was added slowly.

The reaction mixture was stirred for 1 hr and allowed to stand over night at room temperature. The separated product was crystallised from benzene gave yellow needles m.p. 202° (1.6 g)

Analysis : Found : C, 43.96; H, 2.014 %.

$C_{14}H_8O_3Br_2$ requires : C, 43.52; H, 2.072 %.

2,4-Dibromo-1-acetoxy-3-methylxanthone (14)

A mixture of (13) (0.2 g), acetic anhydride (6 ml) and pyridine (1 ml) was heated on a water bath for 18 hr. The reaction mixture was worked up as usual. The product crystallised from aqueous alcohol gave (14) as white needles m.p. 190° (0.1 g).

Analysis : Found : C, 44.74; H, 2.834 %.

$C_{16}H_{10}O_4Br_2$ requires : C, 44.85; H, 2.336 %

Bromination of 1-hydroxy-3-methylxanthone with NBS

1-Hydroxy-3-methylxanthone (2.2 g) was dissolved in CCl_4 (200 ml), to this NBS (2 g) and few crystals of benzoyl peroxide were added, the reaction mixture was refluxed for 10 hr volume of CCl_4 was reduced to 50 ml by distillation. The separated product was filtered off and washed with hot water (5x50 ml). The product crystallised from benzene gave yellow shining needles m.p. 202°C (mix m.p. with (13) showed no depression).

Analysis : Found : C, 44.69; H, 2.439 %.

$C_{14}H_8O_3Br_2$ requires : C, 43.52; H, 2.072 %.

1-Hydroxy-2-bromo-3-methylxanthone (15)

1-Hydroxy-3-methylxanthone (2.0 g) was dissolved in acetic acid (100 ml), warmed up to 50°, pyridine hydrobromide perbromide (3.2 g, 0.01 mol) was then added. The reaction mixture was stirred for 30 min and diluted with water, the product obtained was crystallised from alcohol and benzene mixture yielded pale greenish colour needles m.p. 186-8° Yield (1.8 g).

Analysis : Found : C, 55.08; C, 3.101 %.

$C_{14}H_9O_3Br$ requires : C, 55.26; C, 2.90 %.

Acetate (15A) (AC_2O/pyridine) m.p. 155°.

Analysis : Found : C, 55.31; H, 3.563 %.

$C_{16}H_{11}O_4Br$ requires : C, 55.33; H, 3.17 %.

1-Methoxy-3-methyl-4-bromoxanthone (16)

1-Methoxy-3-methylxanthone (4.5 g) was dissolved in carbon tetrachloride (150 ml), to this NBS (4 g) and few crystals of benzoyl peroxide were added, the reaction mixture was refluxed for 7 hr, after cooling, the separated product was filtered off, washed with hot water (300 ml), the product obtained was crystallised from aqueous alcohol gave (16) as white needles m.p. 158° Yield (4.4 g).

Analysis :Found : C, 56.52; H, 3.871 %.

$C_{15}H_{11}O_3Br$ requires : C, 56.60; H, 3.459 %.

2-Bromo-3-hydroxy-4-methylxanthone (17)

3-Hydroxy-4-methylxanthone (1.1 g) was dissolved in acetic acid (100 ml) and to this pyridine hydrobromide per bromide (1.6 g) or bromine (0.5 ml in 5 ml acetic acid) was added. The reaction mixture was stirred for 1/2 hr. and then poured into water, separated product was crystallised from dioxan gave (17) as buff coloured powder m.p. 282-4°C (0.8 g).

Analysis : Found : C, 54.99; H, 55.26 %.

$C_{14}H_9O_3Br$ requires : C, 55.26; H, 2.96 %.

2-Bromo-3-acetoxy-4-methylxanthone (18)

A mixture of compound (17) (0.2 g) acetic anhydride (5 ml) and pyridine (1 ml) was heated on a water bath for 10 hr. The reaction mixture was worked up as usual. The product crystallised from aqueous acetic acid gave white needles m.p. 202° Yield (0.15 g).

Analysis : Found : C, 54.86; H, 3.283 %.

$C_{16}H_{11}O_4Br$ requires : C, 55.33; H, 3.17 %.

Condensation of resorcinol with methyl 2-hydroxy-5-bromo-benzoate : (19) and (20)

A mixture of resorcinol (1.1 g; 0.01 mol), methyl-2-hydroxy-5-bromo benzoate (2.3 g; 0.01 mol) and diphenyl ether (5.5 ml) was refluxed for 17 hr. The reaction mixture was then subjected to steam distillation.

The product obtained was washed with sodium bicarbonate solution and then with water. The yellowish green solid thus obtained was chromatographed over silica gel coloumn. Elution with (i) petroleum ether (1000 ml) gave a yellow solid which was crystallised from benzene petroleum ether to give (19) as yellow needles. m.p. 178° Yield 0.6 g.

Analysis : Found : C, 53.93; H, 2.76 %.

$C_{13}H_7O_3Br$ requires : C, 53.79; H, 2.413 %.

Acetate m.p. 196-8° (ii) Further elution with benzene (1000 ml) benzene-chloroform (50:50) (1500ml) and chloroform (1500 ml) gave a cream coloured solid, which crystallised from alcohol or alcohol benzene to give (20) as yellowish white needles m.p. 300-1° Yield 0.4 g.

Analysis : Found :C, 54.23; H, 2.822 % .

$C_{13}H_7O_3Br$ requires : C, 53.79; H, 2.413 %.

3-Acetoxy-7-bromoxanthone (21)

A mixture of compound (20) (0.20 g), acetic anhydride (4 ml) and pyridine (0.2 ml) was heated on a water bath for 15 hrs. The reaction mixture was worked up as usual. It was crystallised from acetic acid as white needles m.p. 145-150°. Yield 0.15 g.

Analysis : Found :C, 54.39; H, 2.996 %.

$C_{15}H_9O_4Br$ requires : C, 54.05 H, 2.70 %.

2,4,7-Tribromo-3-hydroxyxanthone (22)

7-Bromo-3-hydroxyxanthone (0.6g) was dissolved in glacial acetic acid (50 ml) and to this pyridine hydrobromide per bromide (0.650g) was added in one lot. The reaction mixture was stirred for 1/2 hr at room temperature. The product obtained after usual work up, crystallised from dioxan petroleum ether mixture gave (22) as yellow tiny needles m.p. 275°.

The product on acetylation with acetic anhydride and pyridine gave acetoxy derivative (23) which crystallised from acetic acid or aqueous alcohol as yellow needles m.p. 198°.

Analysis : Found : 36.77; H, 1.635 %.

$C_{15}H_6O_4Br_3$ requires : 36.74; H, 1.429 %.

7-Bromo-3-acetoxyxanthone on treatment with pyridine hydrobromide did not give any brominated product.

4,7-Dibromo-3-hydroxyxanthone (24)

7-Bromo-3-hydroxyxanthone (0.6g) was dissolved in chloroform-methanol (10:90, 100 ml), pyridine hydrobromide per bromide (0.6g) was then added in one lot. The reaction mixture was stirred for 1/2 hr at 0-10°C and allowed to stand for 3 hr. chloroform was evaporated on a water bath

and the reaction mixture was diluted with water (200 ml), the separated product was crystallised from alcohol gave (24) as light buff colour shining needles m.p. 245°(0.3g).

Analysis : Found C, 41.97; H, 2.389 %.

$C_{13}H_6O_3Br$ requires : C, 42.39; H, 1.902 %.

(10) V.Jayalakshmi, S.Neelkanthan and T.R.Seshadri; Curr. Sci., 37, 1961 (1968).

(11) J.Santesson and G.Sundhdm., Ark. kermi., 30, 427 (1969); C.A., 70, 106309 t (1969).

(12) R.Kurdukar and N.V.Subba Rao., Proc. Indian Acad. Sci., 57A, 280 (1963).

(13) I.Okabayashi and N.Iwata., Che. Pharm. Bull., 28, 2831 (1980).

(14) E.G.Sundhlom; Tetrahaedron; 34, 577 (1978).

(15) J.A.Elix, H.W.Musidlak, T.Sala and M.V.Sargent; Aust. J. Chem; 31, 145 (1978).

(16) L.Fitzpatrik, T. Sala and M.V.Sargent; J.Chem. Soc. Perkin Trans. I; 85 (1980).

(17) D.K.Bhardwaj, R.K.Jain, S.C.Jain and C.K.Mehta; Indian J.Chem. 17B, 288 (1979).

(18) S.N.Dhar; J.Chem. Soc., 109, 745 (1916).

(19) S.N.Dhar; J.Chem. Soc., 117, 1053 (1920).

(20) A.Lespagnol and J.Dupas., Bull. Soc. Chim., 4, 541 (1937); C.A., 31, 4668 (1937).

(21) S.P.Shanmuganathan; J.Annamalai Univ., 29, 189 (1954); C.A., 50, 7107 (1956).

(22) R.L.Webster, J.Marshall and H.Fallscheer; J.Econ. Ent., 33, 909 (1940); C.A., 35, 1568 (1941).

(23) L.F.Steiner and S.A.Summerland; J.Econ. Ent., 36, 435 (1943), C.A., 38, 450 (1944).

(24) E.J. New Comer; J.Econ. Ent., 36, 344 (1943).

(25) A.B.Sen, A.K.Sen Gupta; J.Ind. Chem. Soc., 32, 619 (1955).

(26) E.G.Davis and E.C.White., J.Urol., 2, 107 (1918); C.A., 12, 2015 (1918).

(27) E.Konig and St.V. Kostanecki; Ber; 1944 (1894).

(28) Y.G.Gaekwad, "Studies in Xanthones" Ph.D. Thesis M.S.University of Baroda, 1976.

(29) S.Mary Elizabeth Englert and S.M.McElvain. J.Am. Chem. Soc; 51, 863 (1929).

(30) C.S.Barnes and J.L.Occolowitz; Aust.J.Chem., 17, 975 (1964).

(31) P.Arends, P.Helboe and J.Moller; Org.Mass. Spectrom. 7, 667 (1973).

(32) I.Granoth and H.J.Pownall; J.Org.Chem. 19, 2088 (1975).