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DEVELOPMENT OF PAPER, CHEMICAL AGENT DETECTOR, 3-WAY LIQUID CONTAINING NON-MUTAGENIC DYES. II-REPLACEMENT OF THE BLUE INDICATOR DYE ETHYL-bis-(2,4-DINITROPHENYL) ACETATE (EDA)

by

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DEFENCE RESEARCH ESTABLISHMENT OTTAWA
REPORT NO. 963

a Anachemia Canada Inc.
b Chemical Detection and Decontamination Section

Canada

June 1988
Ottawa

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ABSTRACT

As reported previously, two of the three dyes used in the Paper, Chemical Agent Detector, 3-Way Liquid have been found to be mutagenic. This report describes the work leading to the replacement of the strongly mutagenic indicator dye EDA which is used in the paper to detect liquid droplets of V-type nerve agents. Candidates from several classes of indicator dyes were examined as possible replacements for EDA. These candidate dyes, either synthesized at DREO or obtained commercially, were taken through various stages of evaluation. The recommended replacement dye for EDA is 3',3",5',5"-tetrabromophenolphthalein ethyl ester (TBPE).

CANADA

RÉSUMÉ

Comme décrit précédemment, deux des trois colorants utilisés dans le Papier Détecteur d'Agents Chimiques Liquides "3-Way" se sont avérés être des colorants mutagènes. Ce rapport décrit le travail conduisant au remplacement du colorant indicateur fortement mutagène EDA et qui est utilisé dans le papier pour la détection de gouttelettes d'agents neurotoxiques de type V. Plusieurs candidats provenant de différentes catégories de colorants indicateurs ont été considérés pour possiblement remplacer EDA. Les colorants considérés, préparés à CRDO ou obtenus commercialement, ont été conduits à différents stages d'évaluation. Le colorant indicateur recommandé pour le remplacement de EDA est l'ester éthylique de la 3',3",5',5"-tétrabromophénolphthaleine (TBPE).

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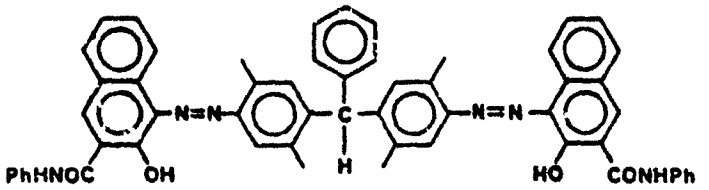
1.0 INTRODUCTION

1.1 BACKGROUND

The Paper, Chemical Agent Detector, 3-Way Liquid, developed in the early 1960's at DREO (1,2) is used by the Canadian Forces and 17 other nations for the detection of liquid chemical warfare agents. Three dyes are incorporated into this paper, each one being capable of detecting a particular family of agents. Thus, with this paper liquid mustard produces a deep red colour with a purple cast, G-type nerve agents produce a yellow colour with a tinge of orange, and V-type nerve agents produce a dark green colour. The dyes presently used are the red dye E (1), the yellow dye A2 (2) and the blue indicator dye EDA (3). The liquid agents dissolve or interact with more than one dye hence the colours produced are different from those that would be produced by the individual dyestuffs.



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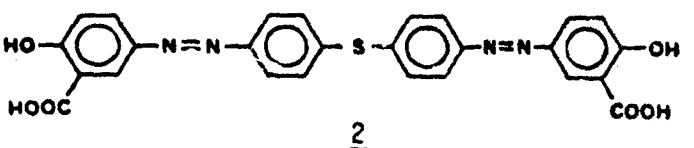
2,5,2',5'-Tetramethyltriphenylmethane-4,4'-diazo-bis-β-hydroxynaphthoic anilide



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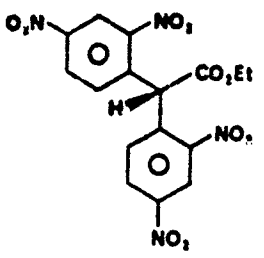
Thiodiphenyl-4,4'-diazo-bis-salicylic acid



3

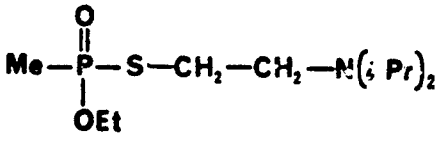
Ethyl-bis-(2,4-dinitrophenyl) acetate

Unfortunately, two of the dyes used in the detector paper have been found to be mutagenic (3). EDA was found to be strongly mutagenic while A2 was moderately mutagenic. Despite the fact that military personnel who attach these papers routinely to their uniforms and equipment have a very low exposure to the impregnated dyes, the problem is crucial for people who are involved in the detector paper manufacturing, i.e. where these dyes have to be handled and ground in kilogram quantities. With mutagenic dyes special protective equipment must be used by industrial workers while manufacturing and grinding the dyes to the required particle size. Special precautions must be taken while loading dye powders into paper-making equipment while the "white water" from the paper making operation can't be dumped until all dye fines are removed. These difficulties have led to a refusal by Canadian industry to continue detector paper manufacture. Therefore, to insure a continuing capability to manufacture the detector paper in Canada, the development of an improved paper containing non-mutagenic dyes was undertaken.

The replacement of the yellow dye A2 was accomplished first and the results are described in a separate report (4). The present report deals with the replacement of the blue indicator dye EDA.

1.2 REQUIREMENTS FOR THE REPLACEMENT OF EDA

EDA is used for the detection of V-agents, for example, VX (4). EDA is an indicator dye and the colour change is pH dependent. In the presence of bases such as VX, the proton attached to the central carbon is removed and the resulting anion, in which the charge is delocalized in the phenyl rings, is an intense blue. In the detector paper, VX not only reacts with EDA but also dissolves some of the yellow dye A2, thus giving a resultant dark green colour.



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A successful replacement candidate for EDA (3) has to fulfill the following requirements:

1) It must be non-mutagenic.

2) The indicator dye must change colour to a very dark green or preferably to dark blue on addition of a base.

3) The pH change of the dye must be low enough to react with VX but also high enough to be compatible with paper making procedures. This range covers approximately pH 4-8.

4) It must be stable enough to give a paper with a good shelf life.

5) It must be soluble in V-agents.

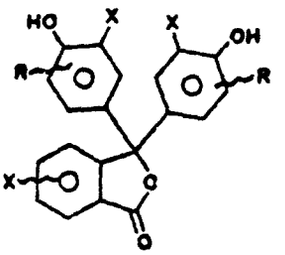
6) It must be insoluble in water at temperatures and pH levels amenable to the manufacture of paper.

7) It must remain solid during the paper drying step (without sublimation) and also during any spray drying procedures which may be required to agglomerate fines. Thus, the melting point must be over 100°C.

8) It must be as inert as possible to chemical substances (such as petroleum products, antifreeze and alcohol solutions) which are found in the field.

1.3 PRELIMINARY WORK

Preliminary work on the replacement of dyestuff EDA was initiated at DREO by Bovenkamp and Lacroix and their results reported in an unpublished summary (5). Over eighteen indicator dyes which were basically phenolphthalein (5) and phenolsulfonephthalein (6) derivatives were investigated. Despite the fact that most of these indicators were in



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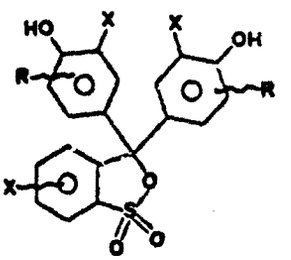
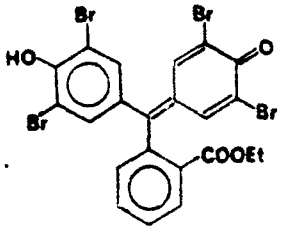


6

the proper pH range and gave an intense blue colour with V simulant[a], only one was found to be a promising candidate. This candidate was 3',3", 5',5"-tetrabromophenolphthalein ethyl ester (7), called TBPE by us, which has the structure shown below. The main reason why the other indicators



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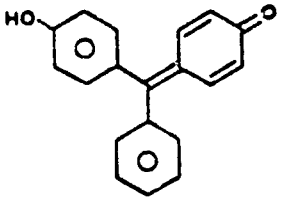
with appropriate pK_a's failed to react with VX was because of their insolubility in the agent. This was demonstrated several times when the dyes were rubbed onto filter paper and VX applied. The VX test spot did not turn blue until a dop of alcohol was added to dissolve the dye.

All the indicators tested in the preliminary study were phenolphthalein (5) (lactone form) or phenolsulfonephthalein (6) (sultone form) derivatives, except for TBPE (7) which possesses the unusual structure of a phthalein alkyl ester. This structural difference very likely accounted for the solubility of TBPE in VX while all the other "normal" phthaleins were not sufficiently soluble. Bovenkamp and Lacroix (6) also prepared and tested phenolbenzein (8) and dibromothymolbenzein (9), both having structures very similar to TBPE with the exception of a



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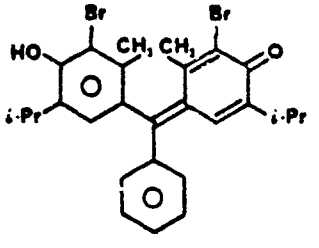

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[a] V simulant is a solution of 5% diethanolamine in methyl cellosolve.

missing ethyl ester, but neither proved to be sufficiently soluble in VX. Therefore, it appears as if the presence of an ester function (as in TBPE and in EDA) is probably a requirement for a successful indicator dye for an organic base such as VX, although this fact has to be proved experimentally.

In the preliminary study, TBPE was found to be the best candidate to replace EDA. This indicator was found to be non-mutagenic (7) and was successfully incorporated into handsheets in the presence of E and A2. The resulting paper on contact with VX gave an immediate blue colour which changed to dark green[a]. Colour responses for the other two dyes were unaffected by the incorporation of TBPE.

Even though TBPE was found to be an excellent replacement for EDA, two major disadvantages were noted:

1) This dye can be obtained commercially but is very expensive due to the complicated five step procedure used to synthesize it. Thus, if it were to be used in the detector paper, the literature synthetic procedure must be simplified (vide infra).

2) TBPE gives a light blue colour with ethanol which is mainly due to the intrinsic low pk value of this dye (colour change, yellow to blue at pH = 3.6 - 4.2). Thus, it would be desirable to have an indicator dye with a slightly higher pk value. Note, however, that the current paper turns yellow with ethanol.

For these reasons, further work was required to determine simpler methods for TBPE synthesis, to synthesize other TBPE analogues with somewhat higher pk values, and to procure and evaluate any other indicator dyes which might be suitable for the replacement of EDA. As can be seen below several diverse classes of indicator dyes were evaluated as possible sources of candidate dyes to replace EDA.

2.0 RESULTS AND DISCUSSION

2.1 APPROACHES FOR THE SYNTHESIS OF TBPE AND ANALOGUES

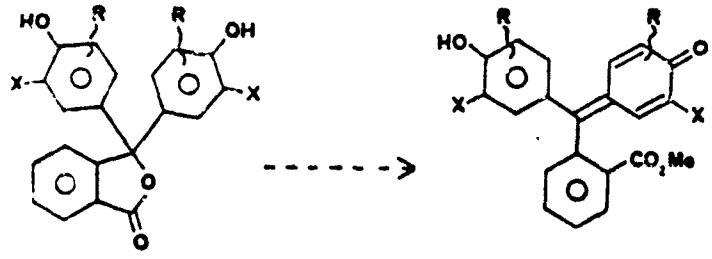
2.1.1 Esterification of phthaleins

Our first approach to the synthesis of TBPE and its analogues was to attempt the esterification of phthalein derivatives 10 to produce the

---

[a] TBPE gives a dark blue colour with VX but since VX also dissolves some of the yellow dye A2 the resultant response is a dark green.

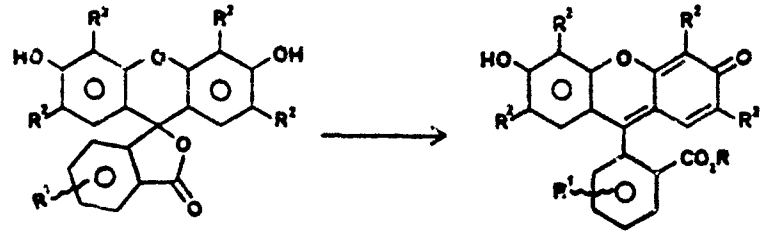
quinoid esters 11 (eq.1). This approach was based on three analogous reactions reported in the literature: the first being the fact that



eq.1

10 11

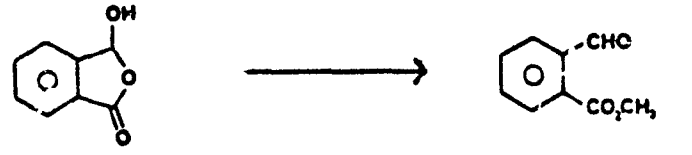
Rose Bengal (12) and derivatives can be easily esterified to the quinoid esters 13 (8) (eq. 2);



eq.2

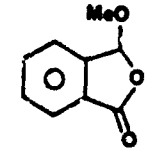
12 13

the second being the esterification of phthalaldehydic acid 14 with diazomethane to produce exclusively the methyl ester 15 (9) instead of the pseudoester 16 (10) (eq. 3); and the third being the direct synthesis



eq.3

14 15



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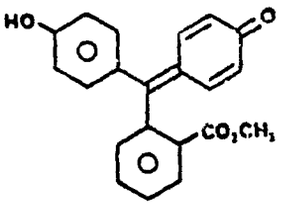
of phenolphthalein methyl ester 17 from the lactone (11) and the same procedure could possibly work for other phthalein derivatives.



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Esterification of several phthaleins were tried and the results are reported in Table 1. This table shows that the esterification of phthaleins with an ethereal solution of diazomethane (entries 1, 5, 7 and 8) did not give the expected compounds. The reactions were either very slow or led to complex mixtures. Upon analysis of the crude products by ^1H NMR and IR there was no evidence for the presence of any phthalein methyl esters. If present, these esters were very minor products since either only starting material was identified or a complex mixture was obtained (except for entry 5). For entry 5, the dimethyl ether 21 (instead of the methyl ester) was found to be the major product.

Table 1 also shows that esterification using the acidic conditions described in the literature (11) for the phenolphthalein methyl ester (17) were not successful either (entries 3, 4 and 6). Even though the reactions appeared to be proceeding as described in the literature (visual observation), ^1H NMR analysis of the crude reaction mixtures showed only starting materials.

Our last attempt was to try the esterification of phenolphthalein (18) using the basic conditions (entry 2) used for the esterification of Rose Bengal (12) (8). Using one equivalent of base, the reaction of phenolphthalein with ethyl iodide gave the monoethyl ether 19 as the main product along with some diethyl ether formation. Addition of more base only led to the formation of more diethyl ether product.

TABLE 1: Attempted Esterification of Phthaleins

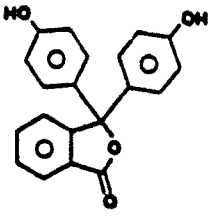
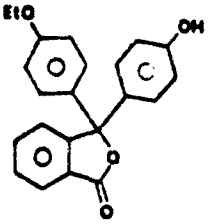
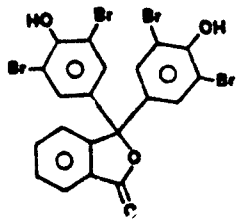
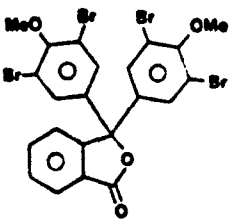
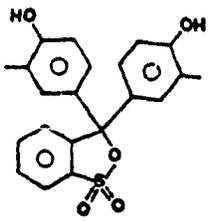
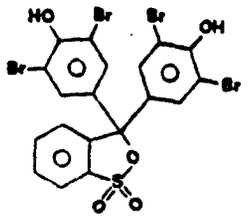
Entry	Phthalein	Method of Esterification	Major Products
1	 phenolphthalein (18)	CH_2N_2	Complex Mixture
2	"	EtI/$NaHCO_3$ (1 eq) acetone-water	 19
3	"	H_2SO_4/EtOH, Δ	No Reaction
4	"	H_2SO_4/HCl (g) MeOH, Δ (11)	No Reaction
5	 3',3",5',5" tetrabromophenol-phthalein (20)	CH_2N_2	 21

TABLE 1 (Cont'd)

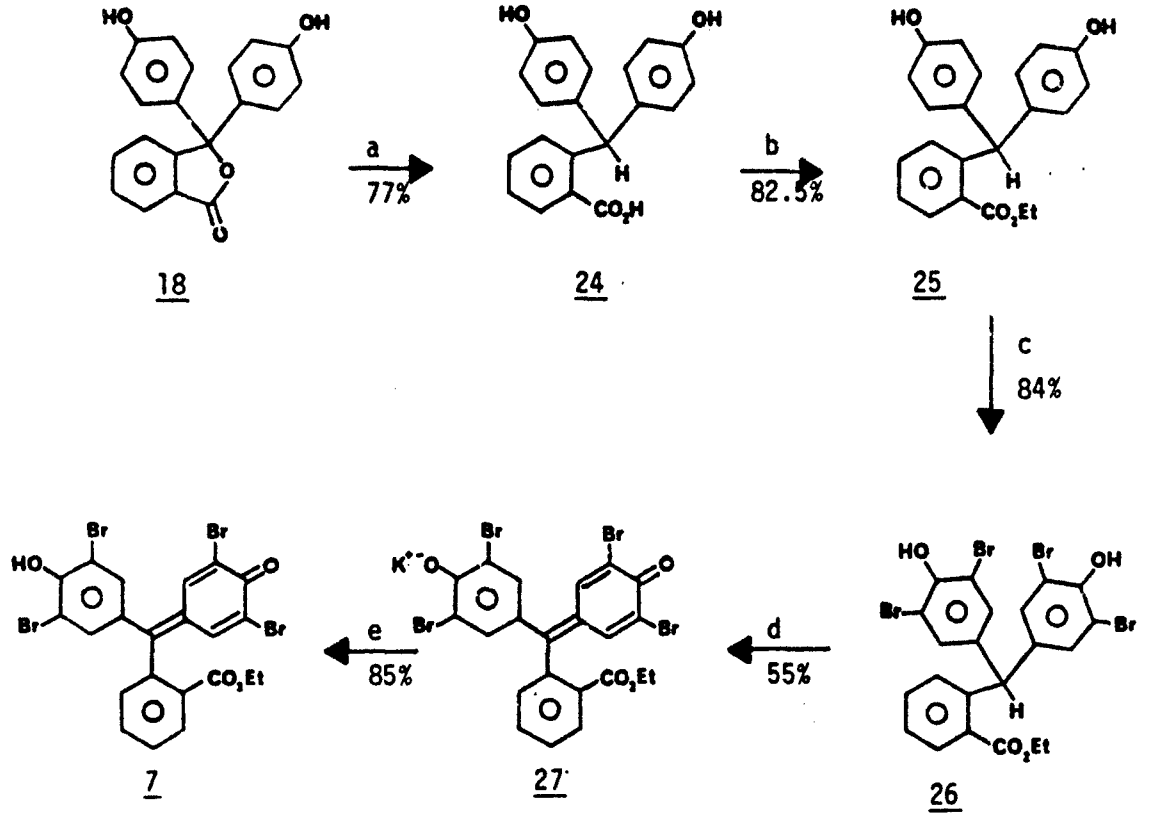
Entry	Phthalein	Method of Esterification	Major Products
6	"	H_2SO_4/HCl (g) MeOH, Δ (11)	No Reaction
7	 cresol red (22)	CH_2N_2	No Reaction
8	 bromophenol blue (23)	CH_2N_2	Complex Mixture

2.1.2 The Development of Improved Procedures for the Synthesis of TBPE and Its Analogues

As mentioned previously, TBPE is a promising candidate for EDA replacement but the synthetic procedure and yields for this compound reported in the literature make it very expensive for incorporation into 3-Way Detector Paper. Our next approach was to carry out a detailed examination of the literature procedure for the synthesis of TBPE and determine if modifications could be made to simplify the synthesis and improve the overall yield. At the same time, we wished to synthesize several other TBPE derivatives with somewhat higher pk values since the pk value for TBPE is on the low side of the desirable range.

The synthesis of TBPE was first described by Davis and Schuhmann in 1947 (12) and their sequence is depicted in scheme 1. Phenolphthalein (18) was reduced with zinc dust in refluxing aqueous sodium hydroxide for

Scheme 1



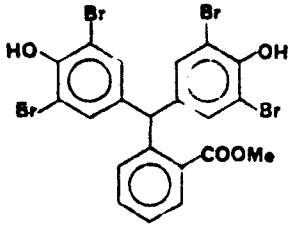
a) Zn powder/NaOH aq., Δ b) HCl(g) /EtOH, r.t. c) Br_2/EtOH, 0°C, 12h
d) K_3FeCN_6/KOH aq, 0°C, 5 min e) AcOH-H_2O/benzene, Δ, 0.5h

1h to produce phenolphthalin (24) in 77% yield. Esterification of this acid using dry hydrogen chloride in ethanol afforded phenolphthalin ethyl ester (25) in 82.5% yield after several days of stirring at room temperature. This was followed by bromination in cold ethanol to give 3',3",5',5"- tetrabromophenolphthalin ethyl ester (26) in 84% yield. Oxidation of the phthalin (26) with potassium ferricyanide in aqueous potassium hydroxide for 5 min afforded the potassium salt of 3',3",5',5"-tetrabromophenolphthalein ethyl ester (27) which was purified by extraction with ethyl alcohol in a Soxhlet apparatus and obtained in a moderate 55% yield. Finally, the potassium salt (27) was suspended in water containing acetic acid and extracted with boiling benzene to give 3',3",5',5"-tetrabromophenolphthalein ethyl ester (7) in 85% yield. Thus the overall yield of 3',3",5',5"-tetrabromophenolphthalein ethyl ester (7) from phenolphthalein (18) was only 25%. In addition to the several days of stirring required in step b and the Soxhlet extraction in step d, the procedure also uses HCl gas and benzene. While such procedures and materials may be used in the laboratory without difficulty, scale up for industrial use may be difficult and in-plant use of large quantities of HCl gas and benzene are frowned upon.

After the publication of the above procedure, a Chinese group reported (13) an improved synthesis of the desired compound (7). The time for the reduction of phenolphthalein (18) (step a) was increased by 1h to give phenolphthalin (24) in 96-100% yield. The time for the esterification (step b) was set at 72h and produced phenolphthalin ethyl ester (25) in 93.5% yield. The conditions for the bromination reaction (step c) were not changed and 3',3",5',5"-tetrabromophenolphthalin ethyl ester (26) was isolated in 88% yield. The oxidation (step d) time was extended for another 5 min and this increased the yield of the potassium salt 27 by 13%. Finally, the acidification-extraction sequence was unchanged and gave TBPE (7) in 85% yield. With these changes, the overall yield of TBPE (7) from phenolphthalein (18) was increased to 45-47%, a significant improvement over the 25% reported by Davis and Schuhmann.

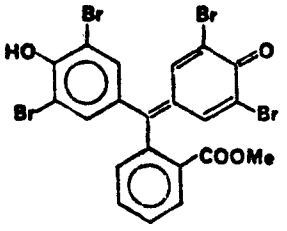
The Chinese sequence was repeated by us with a modification in the esterification step. The reduction (step a) gave phenolphthalin (24) in quantitative yield. The esterification (step b) was performed using sulfuric acid (instead of the undesirable dry hydrogen chloride) in refluxing ethanol for 8-10h and gave phenolphthalin ethyl ester in 98% yield. The bromination (step c) gave compound 26 in 85% yield. The oxidation step was found at the beginning to be very difficult and only 25-30% yield of the desired compound 27 was obtained, compared to the 55% and 68% yields reported by Davis and the Chinese group, respectively. This step was also very tedious. The procedure called for the potassium salt 27 to be purified by extraction with ethyl alcohol using a Soxhlet apparatus before acidification and extraction.

The oxidation step was further investigated using 3',3",5',5"-tetrabromophenolphthalin methyl ester 28 as the model compound. This was prepared in a manner similar to that for the ethyl ester 26. The methyl ester 28 was preferred for this purpose since the reaction mixtures obtained could be more easily analyzed by ^{1}H NMR spectroscopy (vide infra).

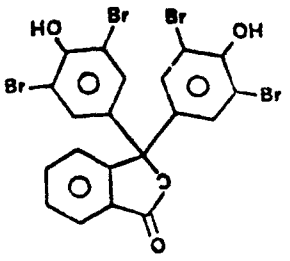


28

Several reaction conditions, as well as different oxidizing agents, were tried. The crude reaction mixtures were neutralized as described above and products analyzed by ^1H NMR spectroscopy. Starting material 28, 3',3",5',5"-tetrabromophenolphthalein methyl ester 29 and 3',3",5',5"-tetrabromophenolphthalein 20 were present in the reaction mixtures in proportions which depended on the reaction conditions. These three



29



20

compounds have characteristic NMR proton chemical shifts (established on authentic samples) which are reasonably well separated from each other in mixtures of the three compounds. Integration of the NMR spectra was used to establish the proportion of each. The results from these studies are reported in Table 2.

Entries 1 to 5 show the relative proportions of compounds 28, 29 and 20 obtained when different quantities of potassium ferricyanide and potassium hydroxide were used along with different reaction times.

TABLE 2: Reaction conditions tried for the oxidation of 3',3",5',5"-tetrabromophenolphthalin methyl ester

Entry	Reaction conditions	Products[a] 28	29	20
1	K_3FeCN_6(2eq), KOH(4eq) H_2O, 0-25°C, 4h	minor	major	major 29/20 = 1:1 mixture
2	K_3FeCN_6(4eq), KOH(8eq) H_2O, 25°C, 5 min	major	major	minor 28/29 = 1:1 mixture
3	K_3FeCN_6(4eq), KOH(8eq) H_2O, 25°C, 10 min	major	minor	major 28/20 = 1:1 mixture
4	K_3FeCN_6(2eq), KOH(2eq) H_2O-MeOH, 30 min then K_3FeCN_6(1eq), KOH(1eq)	-	major	-
5	K_3FeCN_6(2eq), KOH(2eq) H_2O-MeOH, 25°C, 10 min	major	major	- 28/29 = 1.5:1 mixture
6	H_2CrO_4/H_2SO_4(14) acetone	-	-	major
7	H_2CrO_4/AcOH acetone, 25°C, 2h	major (no reaction)		
8	KOH cat/O_2 MeOH, 25°C, 12h	major (no reaction)		
9	N-Chlorosuccinimide, Et_3N(15) CH_2Cl_2, 25°C	complex mixture		
10	MnO_2 act.(16) acetone, 25°C, 12h	major (no reaction)		
11	MnO_2 act. benzene, Δ, 12h	complex mixture		
12	$Ce(NH_4)_2(NO_3)_6$(17) CH_3CN-H_2O, 25°C	complex mixture		

[a] Products were identified by ^1H NMR analysis of the mixtures and the proportions of compounds 28, 29 and 20 were qualitatively established.

Several points are worth noting from the results in Table 2:

- A substantial amount of starting material 28 was generally found in the final reaction mixtures. This phenomenon could be explained by inadequate stirring of the reaction mixtures. A mechanical stirrer was used in both literature procedures (12,13) but because of our small reaction volumes, we used a magnetic stirrer. In later experiments, we also used a mechanical stirrer (vide infra).

- The presence of 3',3",5',5"-tetrabromophenolphthalein 20 in the reaction mixtures clearly indicated the instability of the desired compound 29 in basic media. The formation of compound 20, via the ester saponification of 29 followed by lactonization of the carboxylate ion became very important when excess base or long reaction times were used. When reaction times were kept short and only requisite amounts of base were used the lactone formation almost ceased and only very minor quantities of 20 were found (e.g. entries 2 and 5).

- The conditions used in entry 4 resulted in the desired compound 29 being the major product, however, these conditions were still inadequate since compound 29 could not be isolated in more than 37% yield from the rather complex reaction mixture.

Several other oxidation methods were also tried (entries 6-12) but none proved to be satisfactory since unreacted starting material or complex mixtures were obtained. The only exception was entry 6 where only the formation of lactone 20 was observed. Probably the strong acidic conditions caused the transformation to 20.

Among the different reagents presented in Table 2, alkaline ferricyanide (18) was the only oxidizing agent which gave successful reactions for our system. Since the yields obtained were much lower than those reported in the literature, sufficient 3',3",5',5",-tetrabromophenolphthalin ethyl ester (26) was prepared to try the oxidation with the mechanical stirring technique used in the literature. Using the same proportions and conditions already described (12,13) and prolonging the reaction time to 10 minutes (13), the potassium salt of 3',3",5',5"-tetrabromophenolphthalein ethyl ester (27) was obtained in 89% yield after purification (a 2½ fold increase in yield).

The purification process was also simplified since the extraction of the crude potassium salt 27 with boiling ethanol was done without using a Soxhlet extractor (see experimental). The potassium salt 27 was suspended in water, acidified with acetic acid until the solid changed to a brick red and then extracted with benzene to give TBPE in 81% yield.

Thus, the synthesis of TBPE from phenolphthalein (18) was accomplished in 60% overall yield (a 13-15% increase over the best literature procedure). The conversion of the potassium salt 27 to TBPE was also performed without extracting the desired compound with benzene at the

very end. The brick red solid was simply filtered and air dried to give TBPE in a similar yield and also in very good purity. This last modification should of course greatly simplify the synthesis of TBPE on an industrial scale.

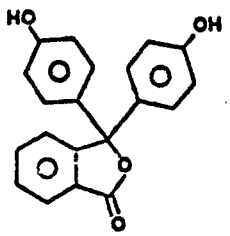
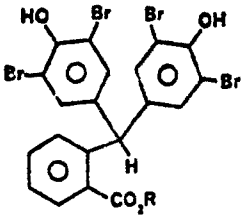
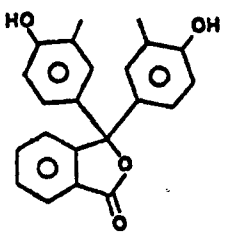
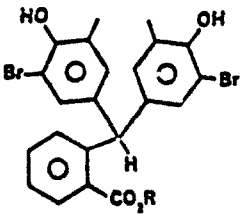
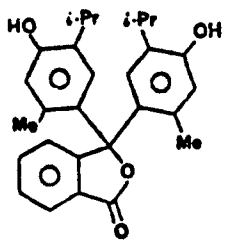
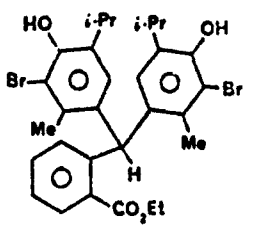
Several other phthalins were also synthesized using the sequence described in scheme 1 and the results are presented in Table 3. As can be seen, the phthalins were generally obtained in good overall yields from the corresponding phthaleins.

The alkaline ferricyanide oxidation procedure was tried on the phthalins shown in Table 3 and the results are reported in Table 4. All the oxidations reported in this Table were performed using a magnetic stirrer. As mentioned previously, yields might have been better if a mechanical stirrer had been used (vide supra). Even if the oxidation reaction conditions were not optimized, several comments can be made on these results.

Entries 1 to 3 show that increasing the bulkiness of the ester group in 3',3",5',5"-tetrabromophenolphthalin alkyl esters did not improve the yield of the oxidation step. Depending on the ester, yields ranging from only 25% to 33% were obtained. Two cresolphthalins 32 and 33 were also tried (entries 4 and 5) but the yields of the oxidations were very low. The 3',3"-dibromo-o-cresolphthalin methyl ester 32 gave only decomposition products. The corresponding ethyl ester 33 gave the desired 3',3"-dibromo-o-cresolphthalein ethyl ester 38 but in less than 16% yield. This dye was isolated by column chromatography but was still impure as shown by ^{1}H NMR analysis. Oxidation of compound 33 was also carried out using a mechanical stirrer and a more dilute solution but this did not improve the yield and the purity of the final product. It is to be noted, however, that the crude 3',3"-dibromo-o-cresolphthalin ethyl ester (38) gave a dark blue response with V simulant and a dark green response with VX. Finally, oxidation of 3',3"-dibromothymolphthalin ethyl ester 35 was attempted (entry 6). No oxidation to the corresponding phthalein 39 occured. The phthalin 35 was insoluble in aqueous potassium hydroxide and was recovered intact.

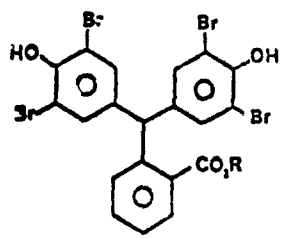
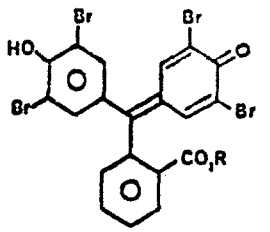
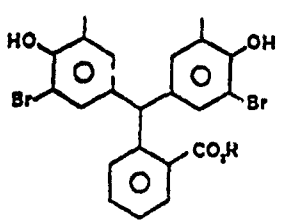
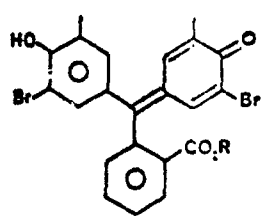
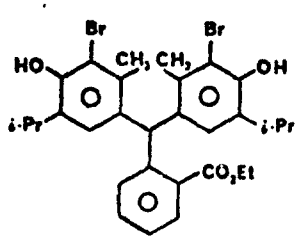
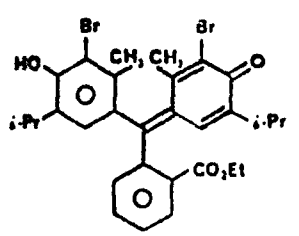
The results presented in this section show that a modified Davis procedure yields TBPE in a satisfactory overall yield. The reduction, esterification, bromination, and oxidation steps can be performed so that yields in the 80-90% region are obtained. In addition TBPE could very likely be produced on an industrial scale at a very reasonable cost since all the materials used in the improved sequence are cheap. The synthesis of other analogues, e.g. cresol and thymolphthalein alkyl esters were not as succesfull since the oxidation step at the end was found to be more difficult.

TABLE 3: Other phthalins prepared

Starting material	Product	Yield
 phenolphthalein (18)		28; R=Me 78% 26; R=Et 61% 30; R=iPr 45%
 o-cresolphthalein (31)		32; R=Me 72% 33: R=Et 50%
 thymolphthalein (34)	 35	*

* - available from earlier work (19).

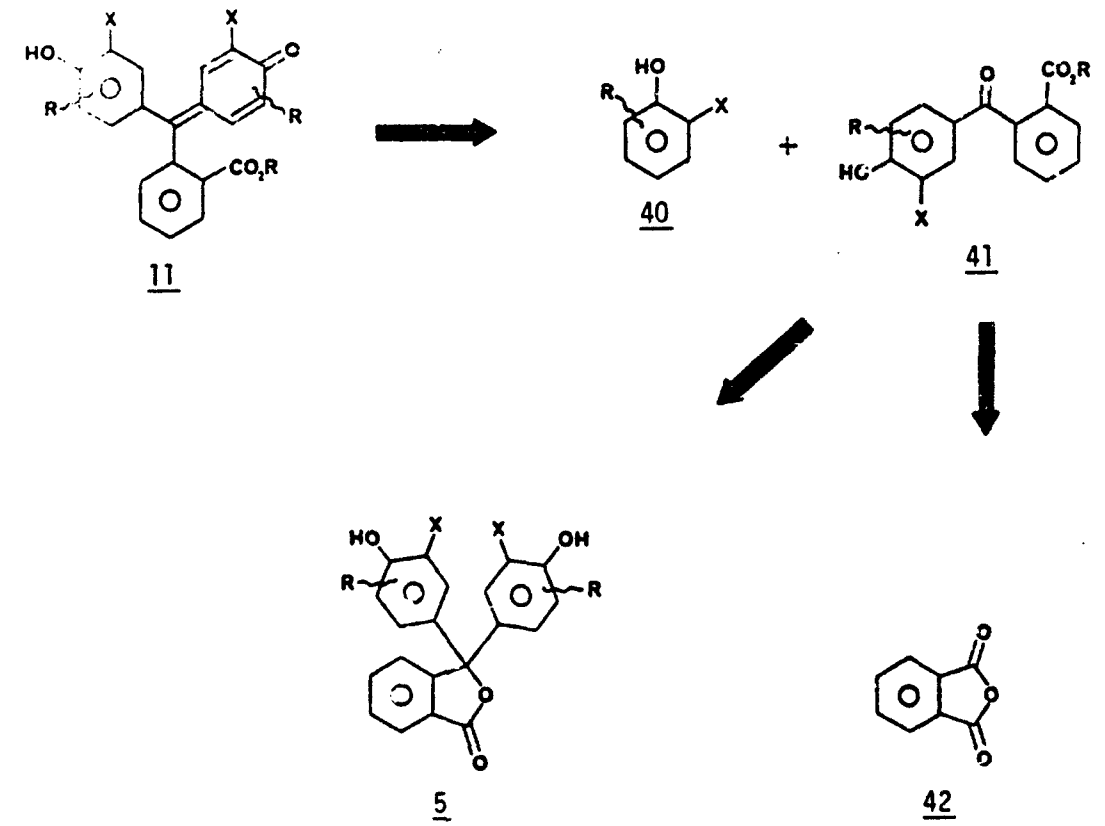
TABLE 4: Oxidation of several phthalins with alkaline ferricyanide

Entry	Starting phthalin	Phthalein
1	 **28**; R=Me	 **29**; R=Me, 29%
2	**26**; R=Et	**7**; R=Et, 25%
3	**30**; R=iPr	**36**; R=iPr, 33%
4	 **32**; R=Me	 **37**; R=Me, 0%
5	**31**; R=Et	**38**; R=Et, <16%
6		 **39**

2.1.3 The benzophenone approach

The other approach for the synthesis of TBPE and analogues 11 was based on the retrosynthetic analysis depicted in scheme 2. As can be seen, analogues 11 could arise from the condensation of a phenol derivative 40 on a benzophenone 41. This benzophenone 41 could be prepared from the Friedel-Crafts acylation of phenol 40 and phthalic anhydride 42 or simply from the corresponding phenolphthalein derivative 5 using the Friedlaender method (20-21).

Scheme 2

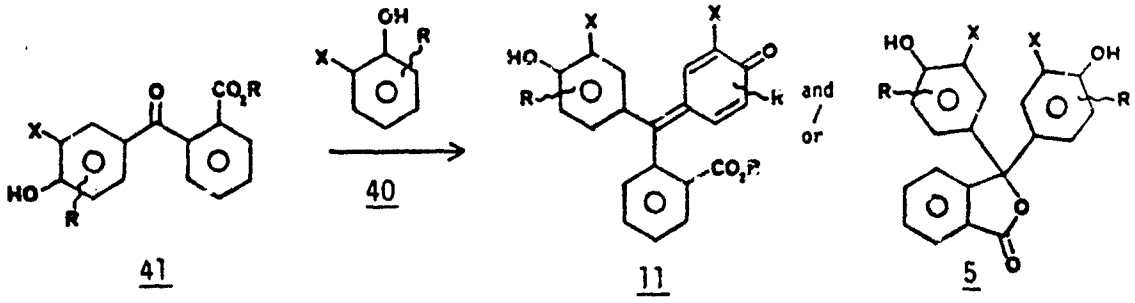


This approach is also a multistep sequence but, if successful, it has two main advantages over that described in the preceeding section.

1) Different R or X groups can be introduced in two different steps (from the synthesis of 40 or 41), which is highly desirable for a versatile synthesis of TBPE derivatives 11.

2) The condensation reaction between the benzophenone derivative 41 and phenols 40 gives the expected compound 11 directly, avoiding the oxidation step required in the previous approach.

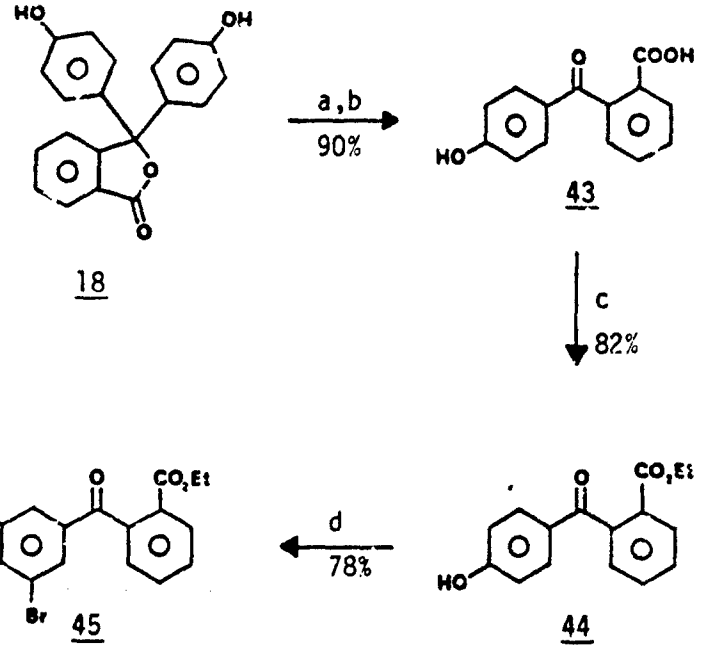
One possible problem that could arise during the condensation is lactone formation which would lead to phenolphthalein derivatives 5 instead of 11 (eq.4).



eq.4

The synthesis of the benzophenone precursor 41 was undertaken as described in scheme 3. Phenolphthalein (18) was first treated with hydroxylamine hydrochloride and the corresponding "phenolphthalein oxime" treated (without isolation) with aqueous sulfuric acid to produce, via a Beckmann rearrangement, 2-(4-hydroxybenzoyl)-benzoic acid (43) in 90% yield (21). Esterification using sulfuric acid in refluxing ethanol afforded the ethyl ester 44 in 82% yield followed by bromination in cold ethanol to produce the dibromo derivative 45 in 78% yield.

Scheme 3



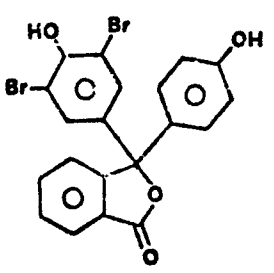
a) $NH_2OH.HCl/H_2O$, 80°C, 15 min b) H_2SO_4 5N, 105°C, 15 min
c) H_2SO_4/EtOH, Δ, 4h d) Br_2/EtOH, 0°C, 1h

Several condensation reactions of 45 with phenol were tried and the results are presented in Table 5.

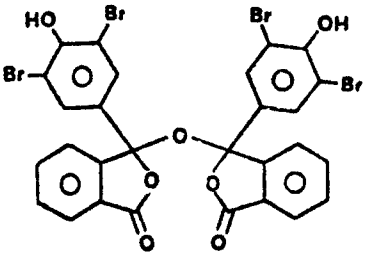
TABLE 5: Condensation of 2-(3,5-dibromo, 4-hydroxybenzoyl)-ethyl benzoate (45) with phenol

Entry	Starting Material	Conditions	Products
1	45	PhOH (1.1eq)/$AlCl_3$ Benzene, Δ, 1h	no reaction
2	45	PhOH/$SnCl_4$ Benzene, Δ, 4h	no reaction
3	45	PhOH (1.1eq)/H_2SO_4 Benzene, Δ, 4h	mixture
4	45	H_2SO_4 Benzene, Δ, 3.5h	dimerization (?)

Initially, the condensation reaction with phenol was attempted using either aluminum chloride (entry 1) or tin tetrachloride (entry 2) as the catalyst. However, only starting materials were recovered even after prolonged refluxing periods. The use of sulfuric acid as a condensing agent (entry 3) led to a mixture from which one compound was found to be the major product by tlc analysis. Interestingly, the same compound was the sole product formed when 45 was treated with sulfuric acid in the absence of phenol (entry 4). This last result automatically ruled out structure 46 and suggested that the compound obtained was the dimer 47.



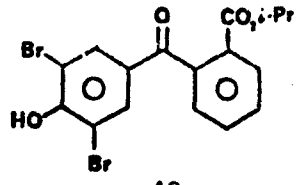
46



47

Similar reactions in which dimers are formed have been reported for compound 43 (22a) and its 2,4-dihydroxy analogue (22b) (structure not shown). The product obtained from the reaction of 45 with sulfuric acid was purified by column chromatography to give a white solid which had no

indicator properties. The structure shown for 47 was also supported by ^1H NMR (signals in the aromatic region only and absence of peaks attributable to the ethyl ester function) and IR spectroscopy (free OH (3520 cm^{-1}) and 5-membered ring lactone (1770 cm^{-1})). Hence, this result clearly indicated that saponification of the ester function of compound 45 was the first reaction to occur and did not give the desired phenolphthalein ethyl ester (e.g. 11). To possibly circumvent or slow down the saponification reaction, compound 48 with the larger isopropyl ester, prepared in 36% overall yield from phenolphthalein (18) (see scheme 3) was also studied. Nevertheless, attempted condensation of compound 48 with phenol in the presence of sulfuric acid also caused the saponification of the ester function and thus formation of dimer 47. Thus this approach was abandoned.

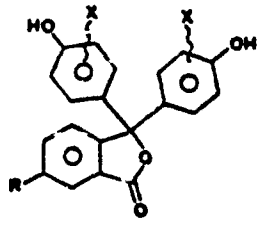


48

2.2 OTHER INDICATOR DYES INVESTICATED FOR THE REPLACEMENT OF EDA

2.2.1 Phenoltrimelliteins

Phenoltrimelliteins are compounds of general structure 49 and are very similar to phenolphthalein (18). The only difference is an extra carboxylic acid function on the phthalide portion. Some trimellitein



49; R=COOH

18; R=H

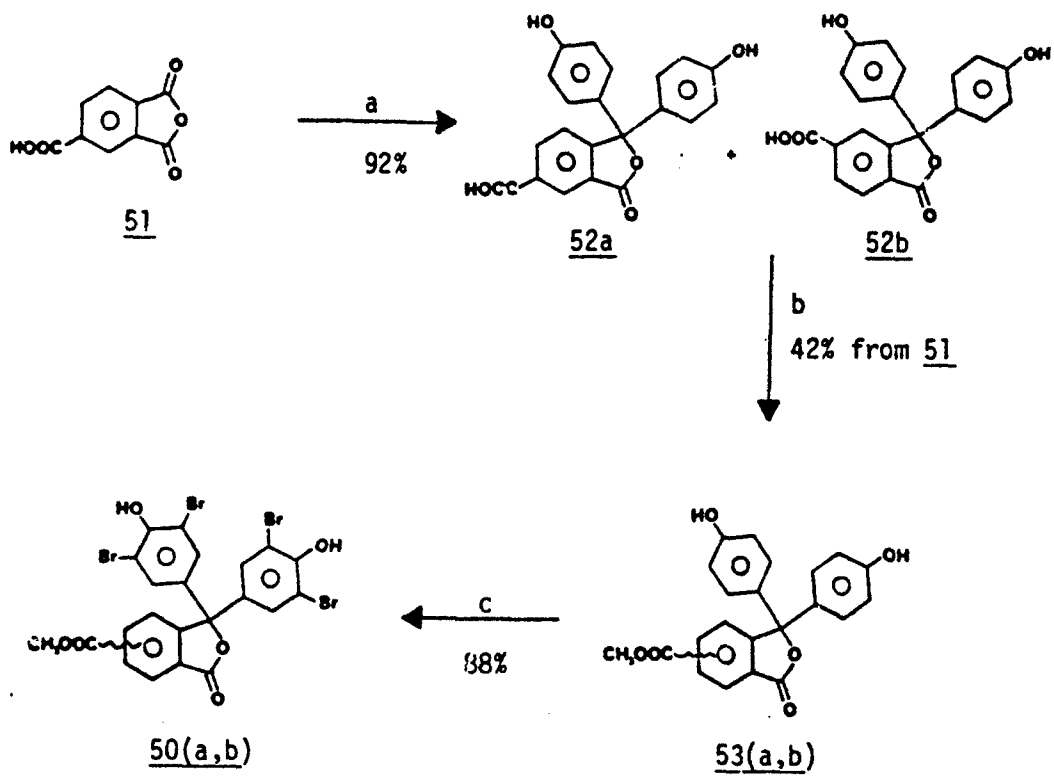
derivatives are known in the literature (23) and are often violet in basic media (pH change from 7.1-10.0). Our interest in these compounds as possible EDA (3) replacements was due to the following reasons:

1) The carboxylic acid group on the phthalide portion can be esterified and should increase the solubility of these dyes in V type nerve agents.

2) The phenol rings can be brominated and should produce derivatives with lower pk values as well as causing the indicator dye to produce the required blue instead of a violet colour.

The target molecule for this approach was 3',3",5',5"-tetrabromophenoltrimellitein methyl ester 50 and its synthesis is depicted in scheme 4.

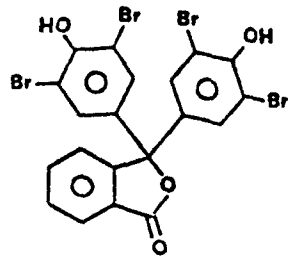
Scheme 4



a) PhOH, $ZnCl_2$, 145°C, 2h b) H_2SO_4/MeOH, Δ, 2.5h
c) Br_2/MeOH, 0-25°C, 0.5h

Starting from commercially available 1,2,4-benzenetricarboxylic anhydride 51, condensation with phenol in the presence of anhydrous zinc chloride gave a brownish solid which was identified as an isomeric mixture of phenoltrimelliteins 52a and 52b. The lack of regioselectivity in the condensation reaction was clearly observed upon esterification of the crude mixture using standard conditions to provide the phenoltrimellitein methyl esters 53(a,b) in 42% overall yield from starting material 51. An analysis of the mixture by ^{1}H NMR spectroscopy showed the presence of two equally intense singlets for the carbomethoxy groups. The inseparable mixture was finally brominated in 88% yield to give the isomeric 3',3",5',5"-tetrabromophenoltrimellitein methyl esters 50(a,b).

The indicator properties of compounds 50(a,b) were very disappointing since no colour was produced with V simulant[a] while only a light blue colour was observed with aqueous sodium hydroxide. These results clearly indicated that compounds 50(a,b) have pk values too high for our purpose and possess poor indicator properties in terms of colour response. A similar behaviour to this was also observed for 3',3",5',5"-tetrabromophenolphthalein (20), (colourless to blue, pH change 7.6-9.4) since this dye turned only light blue with aqueous sodium hydroxide and remained unchanged on contact with V simulant. Thus, the presence of an ester function on the phenoltrimellitein 50(a,b) (the only difference in structure between 50(a,b) and 20) had no or very little influence on the overall reactivity with bases.

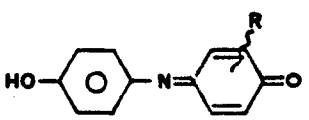


20

[a] V simulant consists of a 5% solution of diethanolamine in methyl cellosolve. This simulant, which produces the same colour on the current detector paper as VX, is actually more basic than VX itself. Since compound 50(a,b) did not produce any colour with simulant, no test was performed with VX.

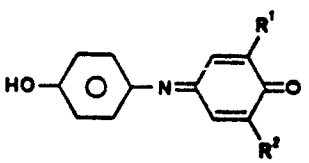
2.2.2 Indophenols

During our work on EDA (3) replacement, a brief investigation was carried out on indophenol type dyes. Indophenols (24) have the general structure 54 and are known to give deep blue colours in basic media.



54

Three indophenols were investigated, namely indophenol (55) itself, 2,6-dichloroindophenol (56) and 2-carbomethoxy indophenol (57). Compounds 55 and 56 were obtained commercially as the sodium salts and converted to their neutral form by acidification while compound 57 was prepared according to the procedure of Vittum and Brown (25).



55; $R^1 = R^2 = H$

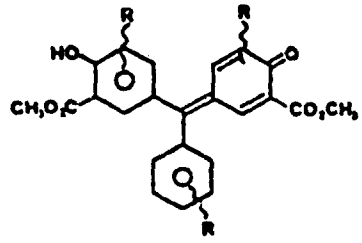
56; $R^1 = R^2 = Cl$

57; $R^1 = COOMe$, $R^2 = H$

Despite the fact that all three indophenols gave a very dark blue response with V simulant, these indicators were found to be of limited use because of their general instability (24). These results prompted us to abandon this approach.

2.2.3 Triphenylmethane indicator dyes

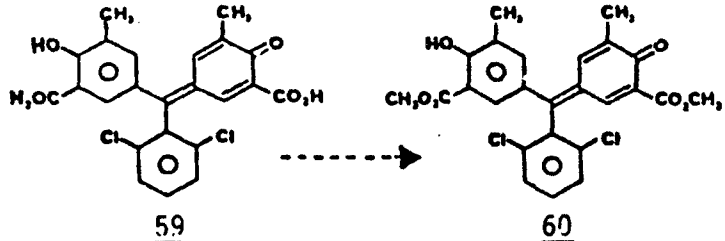
Triphenylmethane indicator dyes of general structure 58 were also considered as possible candidates for EDA (3) replacement. Those compounds have similar structures to TBPE (7) but in this case two ester groups are located on the phenol rings instead of being on the phthalide portion. These esters are also placed in such positions that the lactonization problem encountered previously for TBPE (7) (vide supra) can not occur.



R=H, alkyls, halogens, electron withdrawing groups and combinations

58

Several compounds having general structure 58 are known in the literature (26,27), as exemplified by Mordant Blue 1 (59) and are often violet to blue in basic media. Like many other triphenylmethane indicator dyes having this carbon skeleton, Mordant Blue 1 (59) is a diacid. Since the diester derivative is required for the purpose of EDA (3) replacement, it was felt that the desired diester 60 could be obtained by either

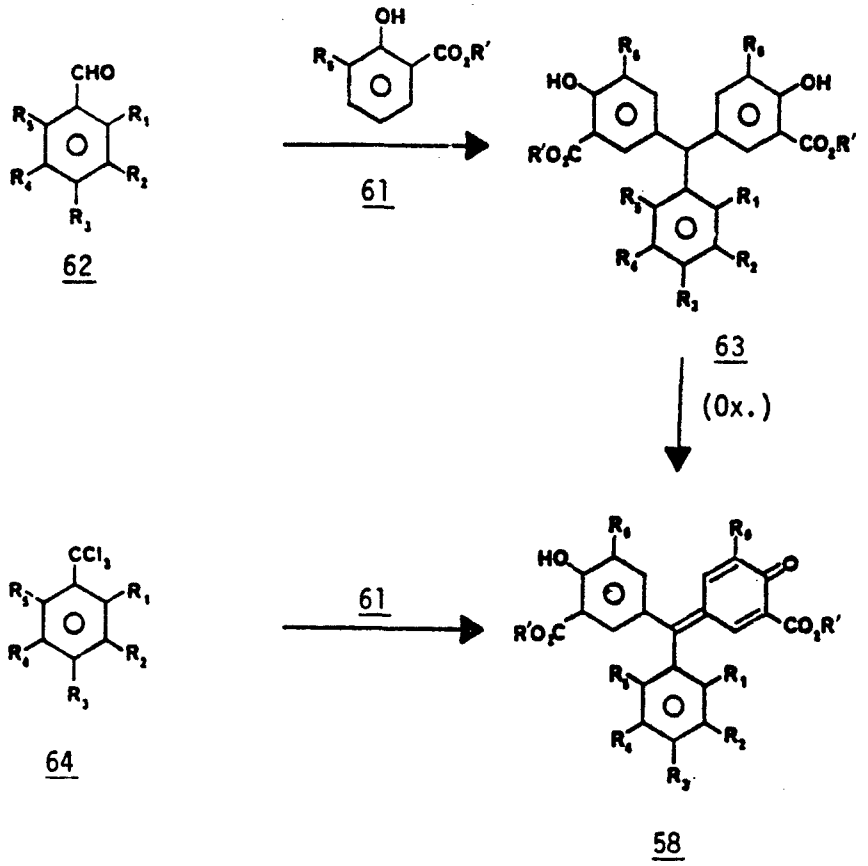


59 60

esterification of compound 59 or by a general synthesis of these compounds.

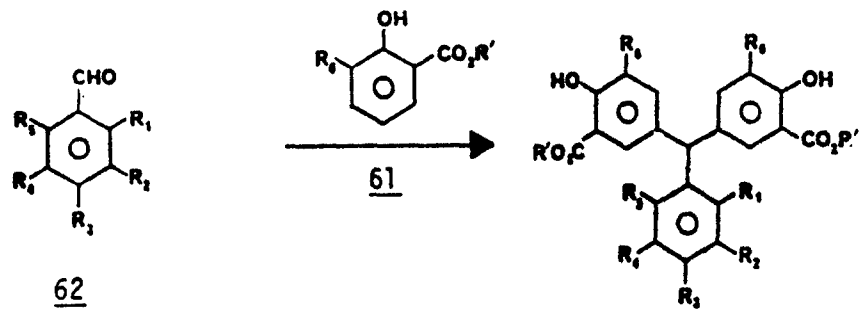
Triphenylmethane indicator dyes are usually prepared (26) (scheme 5) by condensation of a salicylic acid derivative 61 (R'=H) with a substituted benzaldehyde 62 to form triphenylmethane intermediates 63 (leuco bases) followed by oxidation to the desired compounds 58. In this approach, a methyl salicylate derivative 61 (R'=Me) can also be used and would furnish compound 58 (R'=Me; see scheme 5) as the diester form. Triphenylmethane indicator dyes can also be prepared in a single step by condensation of a salicylic acid derivative (61, R'=H or Me) with a substituted benzotrichloride 64.

Scheme 5



The first approach requires a condensation reaction followed by an oxidation step a. 4 is somewhat longer than the straightforward second approach. In order to investigate a variety of candidates, the first approach was preferred since substituted benzaldehydes 62 were more easily available as starting materials than substituted benzotrichlorides 64. Several triphenylmethanes of general structure 63 were prepared and are listed in Table 6. As can be seen, the condensation reactions were, in general, easily accomplished and led to triphenylmethane intermediates in

TABLE 6: Triphenylmethane intermediates prepared

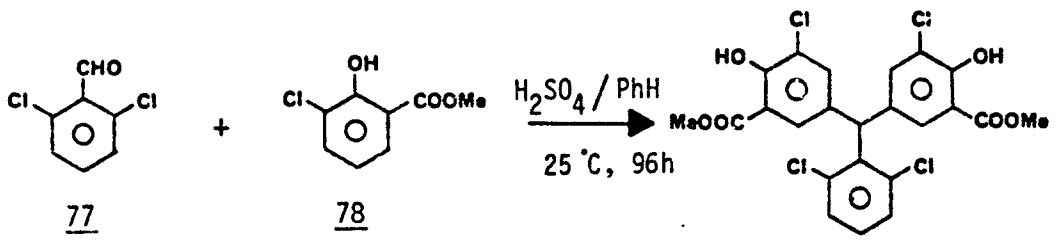


62

63

Entry	Structure No.	Substituents							Yield (%)
		R_1	R_2	R_3	R_4	R_5	R_6	R'	
1	65	H	H	H	H	H	CH_3	CH_3	47
2	66	Cl	H	H	H	Cl	CH_3	CH_3	58
3	67	Cl	H	Cl	H	H	CH_3	CH_3	81
4	68	H	H	NO_2	H	H	CH_3	CH_3	61
5	69	NO_2	H	H	H	H	CH_3	CH_3	57
6	70	Cl	H	H	NO_2	H	CH_3	CH_3	41
7	71	H	H	CN	H	H	CH_3	CH_3	51
8	72	Cl	Cl	H	Cl	H	CH_3	CH_3	73
9	73	Cl	Cl	H	H	Cl	CH_3	CH_3	63
10	74	Cl	H	Cl	H	Cl	CH_3	CH_3	74
11	75	Cl	H	H	H	Cl	Cl	CH_3	15
12	76	Cl	H	H	H	Cl	Br	CH_3	13

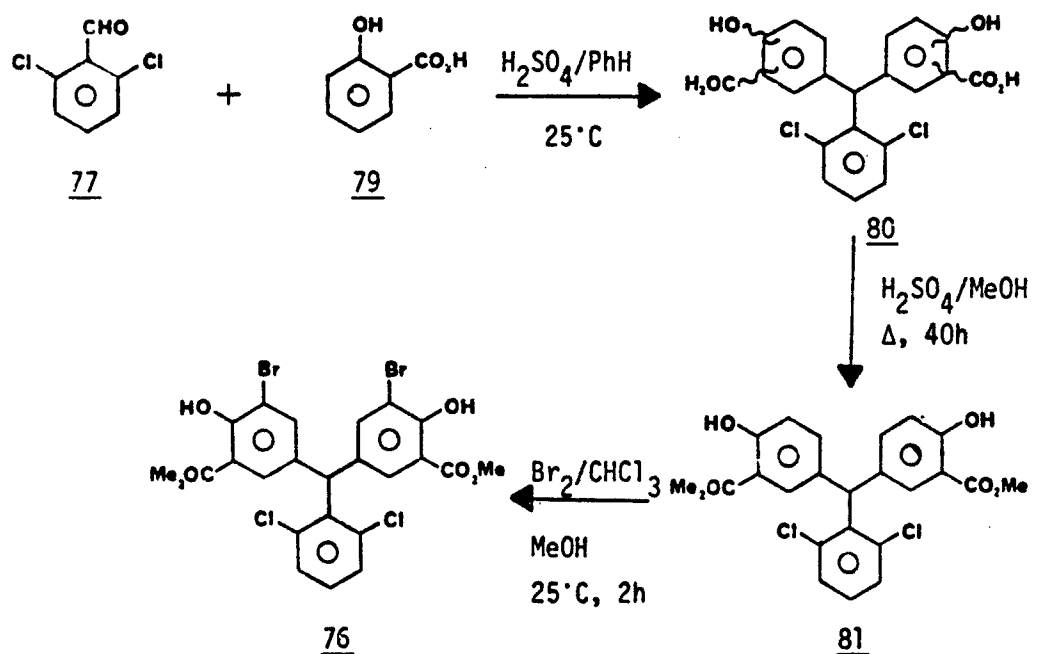
moderate to good yields. Entries 1 to 10 are the condensation products derived from methyl cresotate (61, R'=R_6=Me) and substituted benzaldehydes 62. Methyl cresotate (61, R'=R_6=Me) was used initially since this compound has both ortho positions blocked so the condensation reaction could occur only at the para position. Nevertheless, as the investigation of triphenylmethane indictor dyes progressed several other intermediates were needed (vide infra), especially those with halogens on the salicylic acid moiety (entries 11 and 12). Compound 75 was obtained from the condensation of 2,6-dichlorobenzaldehyde 77 with 3-chlorosalicylic acid methyl ester 78 (eq.5), this last compound being prepared from the esterification of the commercially available 3-chlorosalicylic acid (see experimental part). The



77 78 75 eq.5

desired product 75 was obtained in only 15% yield, because of the very low reactivity of the ester 78 compared to methyl cresotate 61 (R'=R_6=Me). Compound 76 was obtained from a different method (scheme 6). Salicylic

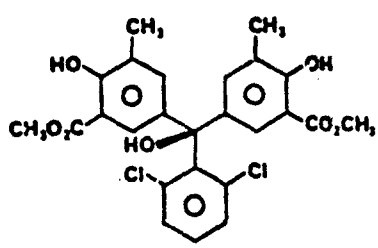
Scheme 6



77 79 80 81 76

acid 79 and 2,6-dichlorobenzaldehyde 77 were first condensed together to give a mixture of triphenylmethanes 80 in which the product of para coupling predominated. The mixture was esterified using the usual method (H_2SO_4/MeOH,Δ) during which the desired isomer 81 precipitated out of the reaction mixture. The overall yield of compound 81 was only 15% from starting aldehyde 77. Finally, compound 76 was obtained in 89% yield from bromination of the diester 81 using methanol and chloroform as cosolvents.

The remaining step in the sequence was the oxidation of the triphenylmethane intermediates previously synthesized to furnish triphenylmethane indicator dyes of general structure 58. Intermediate 66 was chosen as a model compound for the preparation of the indicator dye 60. Several oxidizing agents were tried to compare their effectiveness and the results are presented in Table 7. As reported in the literature (27), nitrosylsulfuric acid and nitrous acid are the most frequently used oxidizing agents in the synthesis of triphenylmethane indicator dyes. In our case, the use of nitrosylsulfuric acid (entry 1) caused partial saponification of the ester groups. The mixture obtained had to be reesterified with an ethereal solution of diazomethane and subsequently purified by column chromatography to furnish the desired compound 60 in 35% yield. The partial hydrolysis of the ester functions was caused mainly by the presence of moisture under the very acidic reaction conditions. Oxidation of compound 66 using nitrous acid (27,28) (entry 2) gave a red solid without indicator properties. The compound isolated from the reaction was identified as the carbinol 82 (vide infra) and not the desired compound 60.



82

The use of ceric ammonium nitrate (29) (entry 3) and chloranil (31) (entry 5) as oxidizing agents gave complex mixtures. Silver oxide (30) (entry 4) as the oxidizing agent afforded compound 60 in 40% yield. Finally, the use of potassium permanganate in refluxing chloroform (32) (entry 6) was tried but the reaction was too slow for our purpose.

TABLE 7: The reaction of compound 66 with several oxidizing agents

Entry	Oxidation Conditions	Product
1	1) HO-S(=O)(=O)-ONO/H_2SO_4 (27) 2) 48h, R.T. 3) Chromatography	60 (35%)
2	$NaNO_2/H_2SO_4$ (28) 25°C/20h	red solid (50%) no indicator properties
3	$Ce(NH_4)_2(NO_3)_6$ (29) CH_3CN, R.T.	complex mixture
4	Ag_2O/benzene (30) Δ, 72h	60 (40%)
5	Chloranil (31) $CHCl_3$, Δ, 24h	complex mixture
6	$KMnO_4$ (s) (32) $CHCl_3$, Δ, 14d	60 (very slow reaction)

Table 7 shows that the oxidation of triphenylmethane intermediate 66 was best performed using silver oxide as the oxidizing agent. Oxidations of other intermediates were tried using this method. The results are reported in Table 8.

In general, the oxidation reactions listed in Table 8 proceeded well. The reaction progress was monitored by thin layer chromatography and the formation of only one major compound was observed in most cases. Aliquots of the reaction mixture were taken periodically, applied to filter paper and the stains produced, after solvent evaporation, tested with a drop of V simulant. A dark blue response was observed in most of the cases. At the end of the reactions, the compounds were isolated by filtering the reaction mixtures on celite to remove the silver salts followed by solvent evaporation under reduced pressure. The crude indicator dyes were generally obtained sufficiently pure to be used directly for further testing. Some of them, when possible, were purified by column chromatography.

TABLE 8: Oxidation of triphenylmethane intermediates using the silver oxide method

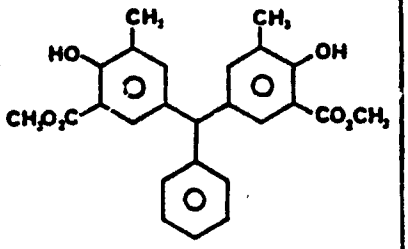
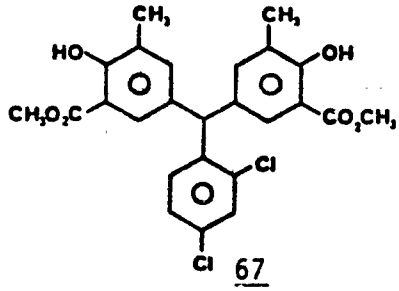
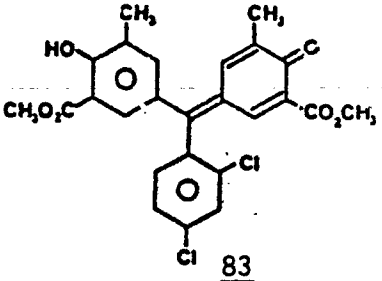
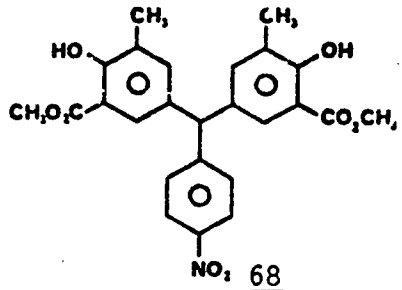
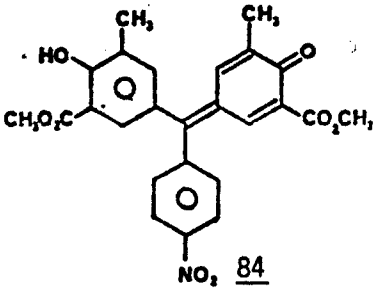
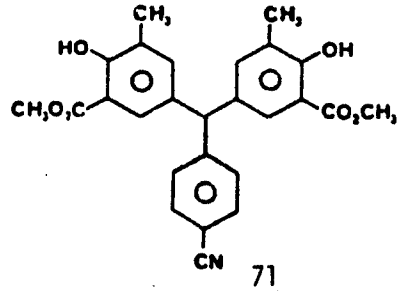
Entry	Starting Material	Conditions	Product	Yield( )
1	 65	1) Ag_2O / $CHCl_3$ Δ, 48h 2) filtration celite	red solid no indicator properties	–
2	 67	1) Ag_2O / $CHCl_3$ Δ, 20h 2) filtration celite	 83	100[a]
3	 68	1) Ag_2O / $CHCl_3$ Δ, 20h 2) filtration celite	 84	(b)
4	 71	1) Ag_2O / $CHCl_3$ Δ, 72h 2) filtration celite 3) chromatography	red solid no indicator properties	82

TABLE 8 (Cont'd)

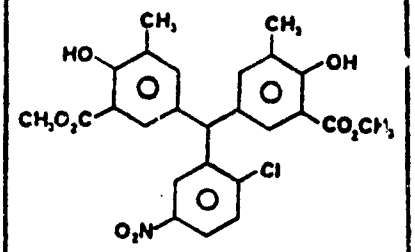
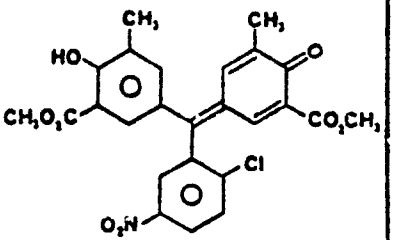
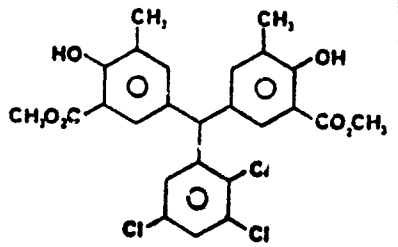
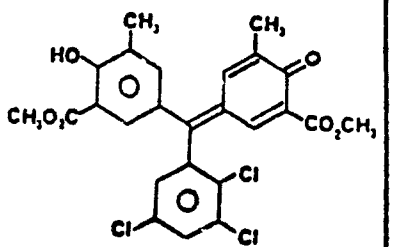
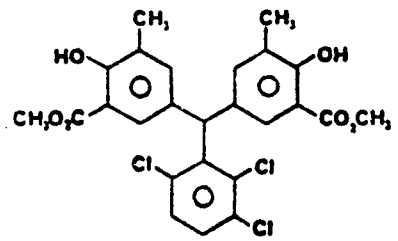
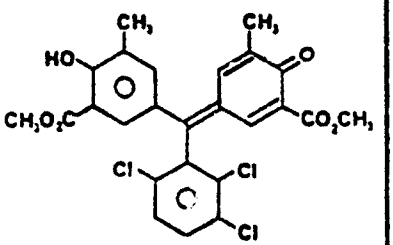
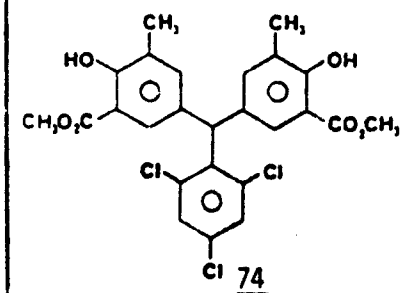
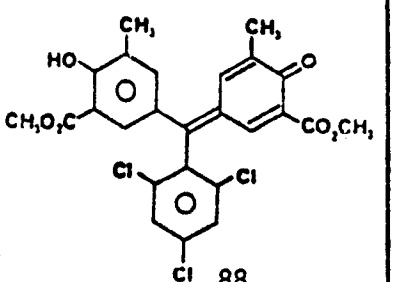
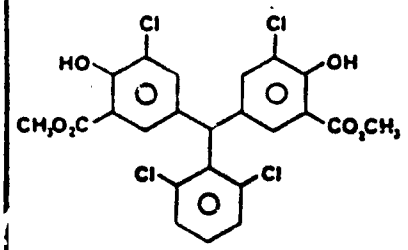
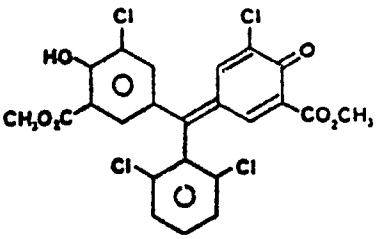
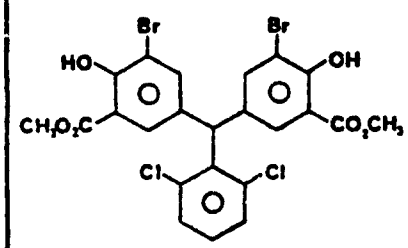
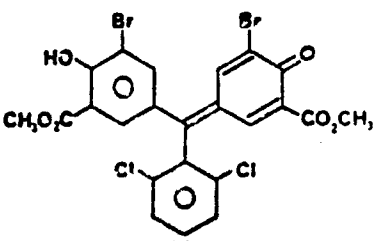
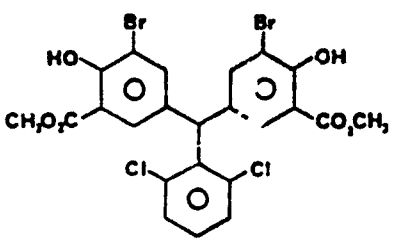
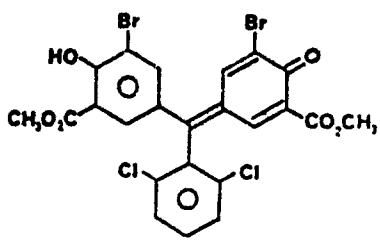
ntry	Starting Material	Conditions	Product	Yield( )
5	 70	1) Ag_2O / $CHCl_3$ Δ, 90h 2) filtration celite	 85	100(a)
6	 72	1) Ag_2O / PhH Δ,3d 2) filtration celite 3) chromatography	 86	71
7	 73	1) Ag_2O / PhH Δ, 5d 2) filtration celite 3) chromatography	 87	75
8	 74	1) Ag_2O / PhH Δ, 3d 2) filtration celite 3) chromatography	 88	66

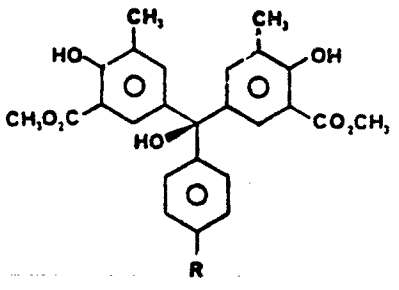
TABLE 8 (Cont'd)

Entry	Starting Material	Conditions	Product	Yield(%)
9	 75	1) Ag_2O / PhH Δ, 16h 2) filtration celite	 89	0
10	 76	1) Ag_2O / PhH Δ, 20h 2) filtration celite	 90	0
11	 76	$Pb(OAc)_4$ PhH, Δ, 2h	 90	94[a]

[a] Yield reported is for the crude compound

[b] Indicator properties lost upon aqueous acidic treatment

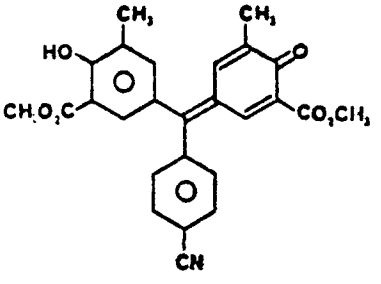
Interestingly, the oxidation of compounds 65 and 71 proceeded as described previously but led, after isolation, to solid materials devoid of any indicator properties. To understand this behaviour, the compound obtained from entry 4 was fully investigated by ^{1}H and ^{13}C NMR spectroscopy in different solvents. Exchange with D_2O was also used in ^{1}H NMR. The structure of the compound isolated was found to be the carbinol 91 and not the desired indicator dye 92. The structure of the compound isolated from entry 1 was also found to be the corresponding carbinol 93. On the other hand, the oxidation of compound 68 (entry 3) gave the desired indicator dye 84. Although its structure was definitely established by ^{1}H NMR spectroscopy, compound 84 was slowly converted to the carbinol 94 upon exposure to air. This explains why compound 84 was further transformed into the carbinol 94 upon an aqueous acidic treatment.



91; R=CN

93; R=H

94; R=NO_2



92

Carbinol formation, which involves the addition of water to the central carbon of the triphenylmethane indicator dye skeleton, was not observed for the oxidation of the other compounds studied. This behaviour can be explained by the presence of substituent(s) located at the ortho position(s) relative to the central carbon atom[a]. Carbinol formation in these cases was retarded or even prevented by the steric hindrance offered by the ortho substituents.

The oxidation of compounds 75 and 76 (entries 9 and 10) using silver oxide failed to give the desired indicator dyes 89 and 90. Decomposition products were obtained instead. Lead tetraacetate, however, was found to be a suitable oxidizing agent for compound 76 and the

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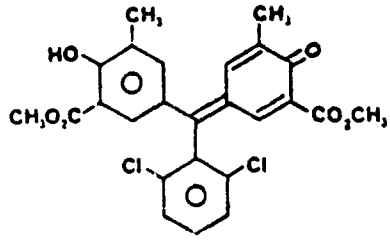
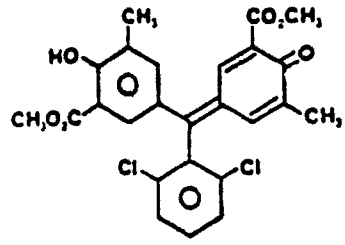
[a] This behaviour is known for aminotriphenylmethane type dyes, e.g. Malachite Green. The same argument can be applied for hydroxytriphenylmethane type dyes although these dyes have been less thoroughly studied (33).

corresponding indicator dye 90 was obtained in 94% crude yield (entry 11). This dye was very difficult to purify and the crude product was used in further evaluation.

Interestingly, all the triphenylmethane indicator dyes synthesized were obtained as a mixture of syn/anti isomers in equal proportions. The phenomenom is exemplified by Mordant Blue 1 dimethyl ester which exists as a mixture of two isomers 60a and 60b.



60a



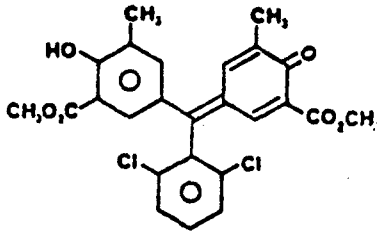
60b

Finally, the properties of the triphenylmethane indicator dyes prepared were determined and the results are reported in Table 9.

By comparison with the indicator properties of EDA (pH change: 8.0-8.4, colourless to blue, dark blue with simulant and VX), the results obtained were quite surprising. Even though several triphenylmethane indicator dyes changed colour in the same pH range as that for EDA or even slightly lower, most of these compounds didn't turn blue on contact with VX. The solubility of these compounds was not the reason for this lack of reactivity since these orange solid materials were readily dissolved in VX.

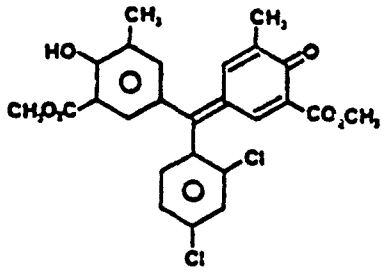
The only exception was compound 90 where a blue response was observed on contact with VX. A sample of 90 was also sent to the Ontario Research Foundation (ORF) for mutagenicity testing using the Ames Salmonella/microsomial mutagenicity plate incorporation assay. Results showed that compound 90 was negative (non-mutagenic) for the five Salmonella tester strains, both in the presence and absence of metabolic activation (34). Compound 90 was then incorporated into handsheets, at 1.5% dye loading, first by itself and then in the presence of E (1) (0.8%) and D.Y.23 (0.6%) (4). The results, presented in Table 10, showed that only a light blue response was obtained for handsheets made of 90 alone (#1625), even at the high dye loading of 1.5%. Three way handsheets (#1626 and #1627) proved to be even worse since only a yellow to light green response was observed on contact with VX. Thus, this indicator dye was unsuitable for the purpose of EDA replacement.

TABLE 9: Properties of the triphenylmethane indicator dyes synthesized[a]



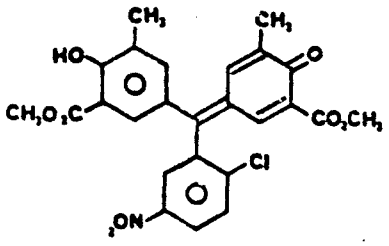
60

m.p.: 205-208°C
pH change: 7.6-8.2 (yellow to blue)
V simulant: dark blue
VX: green



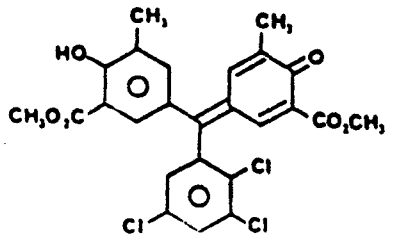
83

m.p.: 145-180°C
pH change: 10.1-11.7 (yellow to blue)
V simulant: dark blue
VX: no colour



85

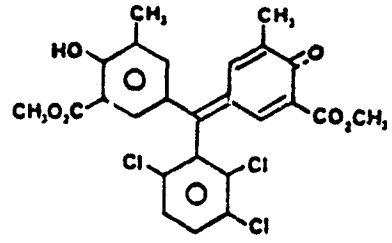
m.p.: 175-185°C
pH change: 7.4-8.0 (yellow to blue)
V simulant: dark blue
VX: no colour



86

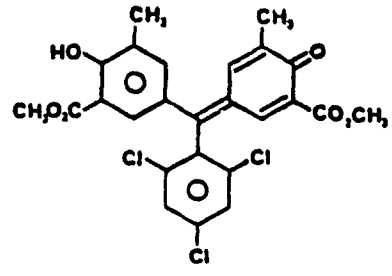
m.p.: 115-175°C
pH change: 9.0-9.6
V simulant: dark blue
VX: no colour

TABLE 9 (Cont'd)



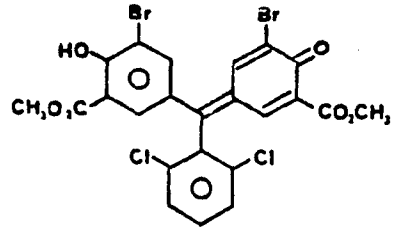
87

m.p.: 80-97°C
pH change: 8.5-9.2
V simulant: dark blue
VX: green



88

m.p.: 214-217°C
pH change: 8.6-9.2 (yellow to blue)
V simulant: dark blue
VX: green



90

m.p.: 148-180°C
pH change: 6.9-7.1
V simulant: dark blue
VX: blue

a The pH change values of the indicator dyes were determined as follows: A 1% solution of the compound to be analysed was made up in a 1:1 (V/V) mixture of ethanol-methanol. A few drops of this solution were added to 50 mL of a 1N hydrochloric acid solution, and this was titrated dropwise with 1N sodium hydroxide. The resultant pH was followed using a pH meter and pH versus colour change was noted. A counter-check of the obtained data was performed by acidifying the basic solution with 1N hydrochloric acid solution to a pH of 1.

TABLE 10: Handsheets of compound 90 tested with VX droplets

Hansheet No.	Dyes incorporated	dye loading (%)	VX response
1625	90	1.5	light blue
1626[a]	E D.Y.23 90	0.8 0.6 1.5	yellow to light green
1627[b]	E D.Y.23 90	0.8 0.6 1.5	yellow to light green

[a] Compound 90 was forced through a #250 mesh screen

[b] Compound 90 was forced through a #325 mesh screen

3.0 CONCLUSIONS

3.1 Many compounds have been prepared and tested as potential replacements for the strongly mutagenic dye EDA. Of all the indicator dyes evaluated, TBPE was the only one found to be an acceptable replacement for EDA.

3.2 A major effort has been devoted to improving the synthetic procedures for TBPE. It can now be synthesized in a higher yield using industrially acceptable processes and chemicals.

3.3 TBPE has been found to give an excellent colour with VX which is as strong or stronger than that obtained with EDA. TBPE has been found to be non-mutagenic (7). The next report (35) presents the successful pilot plant paper run in which TBPE, E and D.Y.23 were used. Full testing results on the final paper is also presented in the next report (35).

4.0 EXPERIMENTAL

4.1 GENERAL

Melting points were measured on a Buchi apparatus and were uncorrected. Infrared spectra were recorded on a Perkin Elmer model no. 283 instrument. High resolution ^{1}H and ^{13}C NMR spectra were obtained using a Varian XL-200 instrument unless noted. Chemical shifts are reported in ppm downfield from tetramethylsilane (TMS) and splitting patterns are designated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), b (broad), bs (broad singlet).

Analytical thin-layer chromatography (tlc) was used frequently to follow the progress of reactions and to assess the purity of compounds. These analyses were performed on aluminum plates precoated with silica gel 60 (Merck F-254) using appropriate solvent systems (vide infra). Compounds were visualized by UV absorption (254 nm), immersion into a phosphomolybdic acid solution followed by heating to 200°C, or by exposure to iodine vapours. The phosphomolybdic solution was made of cerium sulfate (10 g), ammonium molybdate tetrahydrate (25 g), sulfuric acid (100 ml) and distilled water (900 ml).

Flash column chromatography was performed according to the method of Still (36).

TBPE (7) was purchased from Eastman Kodak. All other commercial compounds were obtained from either Anachemia Canada Inc. or Aldrich Chemical Co., Inc. and used without purification.

Handsheets were made according to the procedure described in reference 35.

4.2 SYNTHESIS OF TBPE AND ANALOGUES USING IMPROVED PROCEDURES

Phenolphthalin (24)

Zinc dust (62.5 g, 0.956 mol) was treated with 125 mL of a 25% aqueous solution of ammonium chloride. The slurry was stirred for 15 min, allowed to settle and the liquid decanted. The zinc dust was washed with distilled water (2 x 125 ml) and the washings decanted. The zinc dust was added to a

solution of phenolphthalein (18) (100 g, 0.314 mol) in aqueous sodium hydroxide 10M (160 mL). The mixture was refluxed for 1.5h. During this period, the original dark red solution became colourless. The mixture was cooled to room temperature and filtered to remove the excess zinc dust. The zinc dust was boiled with 200 mL of aqueous sodium hydroxide 6M, filtered off and washed with water. The combined filtrates were poured into aqueous hydrochloric acid 3.6 N (800 mL) to allow precipitation of a white solid. This solid was filtered, washed with distilled water until the washings were neutral to litmus paper and dried (95-100°C, 15 mm Hg, 18h) to give 100.6 g (0.314 mol, 100%) of phenolphthalin 24 as a light pink solid. The product was used in the next step without further purification. It had the following characteristics:

M.p.: 231-233°C (lit(12) 232-236°C); IR(AcOEt): 3700-2900, 1710, 1620, 1600, 1520, 1440, 1370 and 1200-1220 cm^{-1}; ^1H NMR (acetone d-6) δ: 6.66 and 6.92 (2d,8H,AA'BB' system,J=8.5 Hz), 6.79 (s,1H), 7.08 (dd,1H,J=1.6 and 7.5 Hz), 7.19 (dt,1H,J=1.6 and 7.5 Hz), 7.34 (dt,1H,J=1.6 and 7.5 Hz), 7.87 (dd,1H,J=1.6 and 7.5 Hz).

Phenolphthalin ethyl ester (25)

To a suspension of phenolphthalin (24) (100.6 g, 0.314 mol) in absolute ethanol (500 mL) was added sulfuric acid (50 mL) and the mixture was heated to reflux. The reaction progress was monitored by tlc using ethyl acetate-hexane (1:1). After 8h, the mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. The residue then was poured, with stirring, into a mixture of ice and water (300 mL) to precipitate the product. The solid was recovered by filtration and dried under reduced pressure (80°C, 15 mm Hg, 3.5h) to give 106.8 g (0.307 mol, 98%) of compound 25 as a white powder with the following properties:

M.p.: 155-157°C (lit(12) 157-158°C); IR(AcOEt): 3600-3200, 1710, 1620, 1600, 1520, 1440, 1365, 1220, 1175, 1130, 1075 and 1040 cm^{-1}; ^1H NMR (acetone d-6) δ: 1.18 (t,3H,J=7.2 Hz), 4.15 (q,2H,J=7.2 Hz), 6.39 (s,1H), 6.74 and 6.87 (2d,8H,AA'BB' system J=8.6 Hz), 7.03 (d,1H,J=7.4 Hz), 7.28 (t,1H,J=7.4 Hz), 7.42 (dt,1H,J=7.6 and 2.0 Hz), 7.74 (dd,1H,J=7.4 and 2.0 Hz), 8.19 (s,2H,OH).

Tetrabromophenolphthalin ethyl ester (26)

Phenolphthalin ethyl ester (25) (104.8 g, 0.301 mol) was dissolved in absolute ethanol (250 mL) and the solution cooled to 0°C for the slow addition of bromine (72.3 ml, 1.324 mol). The temperature of the mixture was not allowed to rise above 15°C. At the end of the addition, the mixture was stirred at 0°C for 4h and placed in a freezer overnight to allow precipitation. The yellow solid was filtered with suction, washed with the minimum amount of cold absolute ethanol to remove the yellow

colour (excess bromine) and air dried to leave the desired compound 26 as a white solid. The filtrate was reduced in volume under vacuum and placed in the freezer to recover more precipitate and this was treated as before. The recovery process was repeated three times. The total yield was 170.0 g (0.256 mol, 85%) of compound 26 as a white powder.

M.p.: 158-160°C (lit(12) 161-162°C); IR(AcOEt): 3600-3200, 1710, 1550, 1475, 1370, 1225, 1140, 1035 and 730 cm^{-1}; ^1H NMR (acetone d-6) δ: 1.22 (t,3H,J=7.2 Hz), 4.21 (q,2H,J=7.2 Hz), 6.47 (s,1H), 7.13 (dd,1H,J=7.6 and 1.6 Hz), 7.24 (s,4H), 7.40 (dt,1H,J=7.6 and 1.6 Hz), 7.55 (dt,1H,J=7.6 and 1.6 Hz), 7.86 (dd,1H,J=7.6 and 1.6 Hz).

Potassium salt of 3',3",5',5"-tetrabromophenolphthalein ethyl ester (27)

Tetrabromophenolphthalin ethyl ester (26) (10.0 g, 15.1 mmol) was dissolved in an aqueous solution of potassium hydroxide (3.37 g, 60.2 mmol, in 30 mL of water). The resulting solution was cooled at 0°C and stirred mechanically while an aqueous solution of potassium ferricyanide (9.92 g, 30.1 mmol, in 30 ml of water) was added rapidly. After 10 min of vigorous stirring, the dark precipitate which formed in the reaction mixture was filtered with suction and air dried. The solid obtained was treated with absolute ethyl alcohol (400 mL) and heated to a gentle reflux for 0.5h. The mixture was filtered while hot and the solid collected was further extracted with boiling absolute ethanol until the extracts were colourless. The white solid left in the filter (potassium ferrocyanide) was discarded at this point. The filtrates obtained were combined and the solvent was evaporated under reduced pressure to give 9.46 g (13.5 mmol, 89%) of the potassium salt 27 as a dark blue solid. This material was used directly for the next step.

3',3",5',5"-Tetrabromopnenolphthalein ethyl ester (7)

The potassium salt 27 (9.46 g, 13.5 mmol) was suspended in water (100 mL) and treated portionwise with 36% aqueous acetic acid until the colour of the solid changed to a brick red. The mixture was stirred at room temperature for 0.5h and then extracted with benzene (2 x 500 mL). The benzene extracts were combined, washed successively with water (3 x 250 mL) and brine (2 x 250 mL), dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated to give an orange-red solid. After being dried under vacuum (90-110°C, 10 mm Hg), 7.23 g (10.9 mmol, 81%) of the desired compound 7 was obtained as a red solid.

M.p.: 209-211°C (benzene) (lit(12) 209-210°C); IR($CHCl_3$): 3510, 1720, 1645, 1600, 1580, 1475, 1315, 1290, 1170, 1085, 1030, 970 and 940 cm^{-1}; ^1H NMR (acetone d-6) δ: 1.14 (t,3H,J=7.3 Hz), 4.12 (q,2H,J=7.3 Hz), 7.50 (dd,1H,J=7.0 and 2.0 Hz), 7.63 (s,4H), 7.76 (dt,2H, J=7.0 and 2.0 Hz), 8.05 (dd,1H,J=7.0 and 2.0 Hz).
^{13}C NMR (acetone d-6) δ: 14.252, 62.220, 131.324, 131.703, 131.873, 131.958, 132.868, 138.170, 138.449, 138.792, 140.037, 160.555 and 166.465.

The conversion of the potassium salt 27 to TBPE (7) was also performed in the following way: the potassium salt was suspended in water (100 mL), acidified with acetic acid 36% until the solid changed to brick red, the solid filtered with suction and air dried. The desired compound 7 was obtained in a similar yield and had physical data identical to the sample described above. Since this process avoids benzene, it is much more acceptable from an industrial point of view.

All the other phthalins described were prepared according to the reduction-esterification-bromination sequence described above for TBPE. More details are given below along with the physical data of the compounds prepared.

Tetrabromophenolphthalin methyl ester (28)

The esterification of phenolphthalin (24) (8.90 g, 27.8 mmol) was performed in refluxing methanol (80 mL) and sulfuric acid (8 mL) for 20h to give 7.71 g (23.1 mmol, 83%) of phenolphthalin methyl ester as a white solid. The compound was used directly for the next step without further purification.

M.p.: 156-158°C; ^{1}H NMR (acetone d-6) δ: 3.70 (s,3H), 6.30 (s,1H), 6.74 and 6.87 (2d,8H,AA'BB' system, J=7 Hz), 7.05 (d,1H,J=7 Hz), 7.29 (t,1H,J=7 Hz), 7.43 (t,1H,J=7 Hz), 7.75 (d,1H,J=7 Hz), 8.17 (s,2H,OH).

Phenolphthalin methyl ester (9.36 g, 28.0 mmol) in ice cold methanol (40 mL) was then treated with bromine (6.09 ml, 117.7 mmol) for 1h. Tetrabromophenolphthalin methyl ester (28) was obtained as a white solid (12.51 g, 19.25 mmol, 77%).

M.p.: 190-191°C; IR($CHCl_3$); 3520, 1720, 1565, 1475, 1440, 1415, 1330, 1270, 1165, 1135, 1080, 930 and 875 cm^{-1}; ^{1}H NMR(acetone d-6) δ: 3.76 (s,3H), 6.49 (s,1H), 7.16 (d,1H,J=7.4 Hz), 7.25 (s,4H), 7.44 (t,1H,J=7.5 Hz), 7.55 (t,1H,J=7.5 Hz), 7.90 (d,1H,J=7.5 Hz).

Tetrabromophenolphthalin isopropyl ester (30) (12)

The esterification of phenolphthalin (24) (10.0 g, 31.2 mmol) was performed in refluxing isopropanol (100 mL) containing sulfuric acid (8 mL) for 48 h. Phenolphthalin isopropyl ester was obtained as a white solid (6.47 g, 17.9 mmol, 57%). The product was used directly for the next step without further purification.

^{1}H NMR (acetone d-6) δ: 1.16 (d,6H,J=6.0 Hz), 5.01 (m,1H,J=6.0 Hz), 6.39 (s,1H), 6.73 and 6.85 (2d,8H,AA'BB' system, J=7 Hz), 7.03 (d,1H,J=7 Hz), 7.28 (dt,J=7.2 and 1.6 Hz), 7.41 (dt,1H,J=7.2 and 1.6 Hz), 7.73 (dd,1H,J=7.2 and 1.6 Hz), 8.18 (s,2H).

A solution of phenolphthalin isopropyl ester (6.0 g, 16.6 mmol) in ice cold methanol (25 mL) was treated with bromine (3.61 mL, 69.7 mmol) for 0.5 h. Tetrabromophenolphthalin isopropyl ester (30) was obtained as a white solid (9.34 g, 13.77 mmol, 83%).

M.p.: 184-185°C; IR($CHCl_3$): 3515, 1710, 1565, 1475, 1415, 1330, 1270, 1165, 1110, 1080, 930 and 875 cm^{-1}; ^1H NMR (acetone d-6) δ: 1.20 (d,6H,J=6.5 Hz), 5.05 (m,1H,J=6.5 Hz), 6.46 (s,1H), 7.10 (d,1H,J=8.0 Hz), 7.24 (s,4H), 7.39 (t,1H,J=7.6 Hz), 7.53 (t,1H,J=7.6 Hz), 7.85 (d,1H,J=7.6 Hz), 8.54 (s,2H,OH).

Dibromo-o-cresolphthalin methyl ester (32)

The reduction of o-cresolphthalein (31) (6.09 g, 19.91 mmol) was achieved using zinc dust (4.05 g, 61.7 mmol) in refluxing aqueous sodium hydroxide 10M (10 mL) for 1 h. o-Cresolphthalin was obtained as a white powder (6.33 g, 18.12 mmol, 91%).

M.p.: 219-221°C; IR(AcOEt): 3700-2900, 1705, 1620, 1515, 1365, 1230, 1120 and 1040 cm^{-1}; ^1H NMR (acetone d-6) δ: 2.12 (s,3H), 6.57 (s,1H), 6.70 (m,4H), 6.82 (bs,2H), 7.11 (d,1H,J=8 Hz), 7.28 (dt,1H,J=7.6 and 1.6 Hz), 7.43 (dt,1H,J=7.6 and 1.6 Hz), 7.88 (dd,1H,J=7.6 and 1.6 Hz).

A solution of o-cresolphthalin (6.29 g, 18.07 mmol) in methanol (40 mL) was treated with sulfuric acid (5 mL) and refluxed for 3 h to give 5.55 g (15.36 mmol, 85%) of o-cresolphthalin methyl ester as a white powder.

M.p.: 184-186°C; IR(AcOEt): 3700-3200, 1710, 1620, 1515, 1370, 1270-1210, 1120-1080 and 1040 cm^{-1}; ^1H NMR (acetone d-6) δ: 2.12 (s,6H), 3.70 (s,3H), 6.34 (s,1H), 6.68 (m,4H), 6.82 (bs,2H), 7.08 (dd,1H,J=7.6 and 1.6 Hz), 7.27 (dt,1H,J=7.6 and 1.6 Hz), 7.42 (dt,1H,J=7.6 and 1.6 Hz), 7.74 (dd,1H,J=7.6 and 1.6 Hz).

A solution of o-cresolphthalin methyl ester (3.62 g, 10.0 mmol) in ice cold methanol (100 mL) was treated with bromine (1.3 mL, 24.8 mmol) for 1 h. Dibromo-o-cresolphthalin methyl ester (32) was obtained as a white solid (4.67 g, 9.0 mmol, 90%).

M.p.: 172-173°C; IR(AcOEt): 3700-3200, 1715, 1610, 1580, 1490, 1370, 1220, 1190, 1180, 1135, 1115, 1080 and 1040 cm^{-1}; ^1H NMR (acetone d-6) δ: 2.20 (s,6H), 3.75 (s,3H), 6.38 (s,1H), 6.87 (s,2H), 6.98 (s,2H), 7.10 (dd,1H,J=7.6 and 1.6 Hz), 7.34 (dt,1H,J=7.6 and 1.6 Hz), 7.50 (dt,1H,J=7.6 and 1.6 Hz), 7.69 (bs,2H,OH), 7.83 (dd,1H,J=7.6 and 1.6 Hz).

Dibromo-o-cresolphthalin ethyl ester (33)

A solution of o-cresolphthalin (5.00 g, 14.36 mmol) in absolute ethanol (20 mL) containing sulfuric acid (2 mL) was refluxed for 8 h and then stirred overnight at room temperature to give 4.?2 g (11.34 mmol, 79%) of o-cresolphthalin ethyl ester as a white solid.

M.p.: 178-181°C; IR(AcOEt): 3700-3150, 1710, 1620, 1515, 1370, 1225, 1120, 1075 and 1040 cm^{-1}; ^1H NMR (acetone d-6) δ: 1.19 (t,3H,J=7.2 Hz), 2.12 (s,6H), 4.15 (q,2H,J=7.2 Hz), 6.34 (s,1H), 6.70 (m,4H), 6.81 (bs,2H), 7.06 (d,1H,J=7.3 Hz), 7.27 (t,1H,J=7 Hz), 7.41 (t,1H,J=7 Hz), 7.72 (d,1H,J=7 Hz), 8.01 (bs,2H,OH).

o-Cresolphthalin ethyl ester (4.22 g, 11.3 mmol) in ice cold absolute ethanol (40 mL) was treated with bromine (1.27 mL, 23.3 mmol) for 0.5 h to give 4.24 g, (7.91 mmol, 70%) of dibromo-o-cresolphthalin ethyl ester 33 as a light pink solid.

M.p.: 121-122°C; IR(AcOEt): 3600-3200, 1710, 1610, 1580, 1485, 1370, 1325, 1220, 1175, 1130, 1115, 1075 and 1040 cm^{-1}; ^1H NMR (acetone d-6) δ: 1.20 (t,3H,J=7.6 Hz), 2.21 (s,6H), 4.18 (q,2H,J=7.6 Hz), 6.37 (s,1H), 6.86 (d,2H,J=2.6 Hz), 6.98 (d,2H,J=2.6 Hz), 7.08 (dd,1H,J=7.6 and 1.6 Hz), 7.35 (dt,1H,J=7.6 and 1.6 Hz), 7.49 (dt,1H,J=7.6 and 1.6 Hz), 7.82 (dd,1H,J=7.6 and 1.6 Hz).

Dibromothymolphthalin ethyl ester (35)

This procedure is from reference 19 which has not been published. It is included here for completeness.

Thymolphthalein (34) (20.0 g, 46.45 mmol) was reduced with zinc dust (6.92 g, 105.8 mmol) in refluxing aqueous sodium hydroxide 10M (40 mL) for 1 h to give thymolphthalin (18.1 g, 41.85 mmol, 90% yield) as a white powder.

M.p.: 204-206°C; ^1H NMR (60 MHz, acetone d-6) δ: 1.0 (d,12H,J=7 Hz), 2.1 (s,6H), 3.2 (m,2H,J=7 Hz), 6.6 (bs,2H), 6.7 (bs,2H), 6.9 (bs,1H), 7.1 (m,1H), 7.4 (m,2H), 8.0 (m,1H), 8.25 (bs,3H,OH).

A solution of thymolphthalin (18.0 g, 39 mmol) in absolute ethanol (200 mL) was saturated with dry hydrogen chloride (3.5 h) and stirred at room temperature for 7 d. The solvent was evaporated under reduced pressure and the residue obtained poured on ice. The precipitate was filtered, dissolved in ether (50 mL) and the organic layer washed with aqueous sodium carbonate (10%). The ether solution was dried over anhydrous magnesium sulfate, filtered and the solvent evaporated to give thymolphthalin ethyl ester (18.0 g, 39.08 mmol, 84%) as a white powder.

M.p.: 170-174°C; ^{1}H NMR (60 MHz,acetone d-6) δ: 1.0 (d,12H,J=7 Hz), 1.1 (t,3H,J=7 Hz), 2.1 (s,6H), 3.2 (m,2H,J=7 Hz), 4.1 (q,2H,J=7 Hz), 6.5 (bs,2H), 6.6 (bs,1H), 6.7 (bs,2H), 7.0 (m,1H), 7.4 (m,2H), 7.8 (m,2H).

A solution of thymolphthalin ethyl ester (18.0 g, 39 mmol) in absolute ethyl alcohol (60 mL) was cooled to 0°C and treated dropwise with bromine (14.55 g, 90.9 mmol). The mixture was then stirred at room temperature for 3 h and placed in a freezer to allow precipitation. The solid formed was collected by filtration and dried under high vacuum to give dibromothymolphthalin ethyl ester (35) (12.85 g, 20.8 mmol, 53% yield) as a yellowish solid.

M.p.: 108-111°C; IR($CHCl_3$): 3520, 2985, 1715, 1475, 1415, 1280, 1170, 1130, 1080, 1040 and 1020 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.02 (d,12H,J=6.8 Hz), 1.24 (t,3H,J=7.2 Hz), 2.24 (s,6H), 3.17 (m,2H,J=6.8 Hz), 4.11 (q,2H,J=7.2 Hz), 5.65 (s,1H), 6.38 (s,2H), 6.77 (d,1H,J=8.7 Hz), 7.31 (m,2H), 7.80 (d,1H, J=9 Hz).

3',3",5',5"-Tetrabromophenolphthalein methyl ester (29)

Tetrabromophenolphthalin methyl ester (28) (0.5 g, 0.77 mmol) was dissolved in a cold aqueous solution of potassium hydroxide (0.176 g, 3.16 mmol, in 2 mL of water), yielding a light blue solution. The solution was stirred vigorously (magnetic stirrer) while a solution of potassium ferricyanide (0.506 g, 1.54 mmol) in water (1 mL) was added rapidly. After about 10 min, the dark blue precipitate formed was collected by filtration and air dried. The blue precipitate was then suspended in water, acidified with glacial acetic acid until the colour changed to green and the aqueous mixture extracted with benzene (2× 10 mL). The benzene extracts were combined, dried over anhydrous magnesium sulfate, filtered and then the solvent was evaporated under reduced pressure to give a green solid. This solid was shown by tlc (ethyl acetate-hexane 1:1) to be a mixture of two compounds. Purification of the mixture by column chromatography (flash, 3 cm, ethyl acetate) gave a yellow oil (338 mg, 0.52 mmol) (which was identified by ^{1}H NMR to be mainly starting material 28) followed by the desired compound 29 as an orange solid (144 mg, 0.22 mmol, 29% yield).

M.p.: 217-224°C; IR($CHCl_3$): 3030, 1730, 1650, 1600, 1580, 1520, 1475, 1440, 1315, 1290, 1090 and 1030 cm^{-1}; ^{1}H NMR (acetone d-6) δ: 3.66 (s,3H), 7.54 (dd,1H,J=7.2 and 1.4 Hz), 7.63 (s,4H), 7.77 (m,2H), 8.05 (dd,1H,J=6.8 and 1.2 Hz).

3',3",5',5"-Tetrabromophenolphthalein isopropyl ester (36)

Tetrabromophenolphthalin isopropyl ester (30) (1.0 g, 1.47 mmol) was dissolved in a cold aqueous solution of potassium hydroxide (0.336 g, 6.05 mmol in 5 mL of water). This solution was stirred vigorously

(magnetic stirrer) while potassium ferricyanide (0.992 g, 3.01 mmol) in water (5 mL) was added rapidly. After about 5 min, the dark blue precipitate formed was collected by filtration, transferred into an extraction thimble and extracted with boiling absolute ethanol. The ethanol was evaporated under reduced pressure to give 0.91 g of a deep blue solid. This solid was suspended in water (10 mL), diluted with benzene (10 mL) and the resulting mixture acidified with acetic acid. The benzene layer turned orange immediately while the aqueous layer lost its blue colour. The two phases were separated and the aqueous layer extracted again with benzene (10 mL). The benzene extracts were combined, dried over anhydrous magnesium sulfate, filtered and the solvent was evaporated to give 0.87 g of an orange solid. Tlc analysis (ethyl acetate-hexane 1:1) showed that the compound (R_f=0.18) was contaminated with other impurities. The mixture was purified by column chromatography (flash, 4 cm, ethyl acetate) to give the desired compound 36 as a greenish solid (0.333 g, 0.48 mmol, 33% yield).

M.p.: 118-123°C; ^{1}H NMR (acetone d-6) δ: 1.13 (d,6H,J=6.4 Hz), 4.94 (m,1H, J=6.4 Hz), 7.48 (m,1H), 7.63 (s,4H), 7.66-7.76 (m,2H), 7.99 (d,1H, J=2.2 Hz).

4.3 THE BENZOPHENONE APPROACH

2-(4-Hydroxybenzoyl)-benzoic acid (43) (21)

Phenolphthalein (18) (30.8, 96 mmol) was treated with an aqueous solution of sodium hydroxide 2.5N (160 mL) and the mixture heated to 65°C. As soon as the phenolphthalein (18) was dissolved, a solution of hydroxylamine hydrochloride (7.67 g, 106 mmol, in 30 mL of water) was added in one portion. After 5 min, the colour changed from a distinct red to a brownish red. The solution was stirred for an additional 15 min at 75-80°C and poured, while still warm, into aqueous sulfuric acid 0.5N (700 mL). The yellow precipitate which formed was filtered, washed with water until the washings were neutral to litmus paper and air dried.

The yellow "phenolphthalein oxime" was transferred into a 500 mL flask fitted with a magnetic stirrer/heater and a thermometer and treated with a prewarmed (90°C) aqueous solution of sulfuric acid 5N (100 mL). The stirring was started and the yellow slurry was rapidly heated. When the temperature reached 96-102°C, a dark yellow solution resulted which became turbid after 5 min. The reaction mixture was stirrred for an additional 10 min at 96-102°C and cooled to room temperature to allow crystallization. The sandy crystals were filtered, washed with water until the washings were neutral to litmus paper and air dried to afford 20.45 g (84.50 mmol, 88%) of the desired compound 43.

M.p.: 211-214°C (lit(21): 211-215°C); IR(DMSO): 3600-2200, 1710, 1660, 1600, 1515, 1285, 1250, 1175, 1150 and 855 cm^{-1}; ^1H NMR (acetone d-6) δ: 6.90 and 7.62 (2d,4H,AA'BB' pattern, J=9 Hz), 7.38 (dd,1H,J=1.6 and 7.1 Hz), 7.58-7.76 (m,4H), 8.08 (dd,1H,J=1.6 and 7.1 Hz), 9.1 (bs,2H,OH).

2-(4-Hydroxybenzoyl)-ethyl benzoate (44)

To a solution of compound 43 (19.27 g, 79.6 mmol) in absolute ethanol (200 mL) was added sulfuric acid (10 mL) and the mixture heated under reflux for a period of 6 h. The solution was allowed to cool to room temperature and the solvent was removed under reduced pressure. The residue obtained was dissolved in ethyl acetate (200 mL), the solution was transferred into a separatory funnel and then washed with aqueous potassium carbonate 20% until effervescence ceased. The organic layer was then washed with brine, dried over anhydrous magnesium sulfate, filtered and the solvent evaporated under reduced pressure to give a green oil. This oil was coevaporated with carbon tetrachloride (2 x 200 mL) and residual solvents were removed under high vacuum to give the desired compound 44 (17.7 g, 65.6 mmol, 82% yield) as an off-white solid.

M.p.: 106-109°C; IR(DMSO): 3450, 1720, 1660, 1600, 1520, 1285, 1250, 1175, 1155 and 855 cm^{-1}; ^1H NMR (acetone d-6) δ: 1.05 (t,3H,J=7.0 Hz), 4.05 (q,2H,J=7.0 Hz), 6.90 and 7.61 (2d,4H,AA'BB' system, J=8.9 Hz), 7.40 (dd,1H,J=8.0 and 1.9 Hz), 7.57-7.72 (m,2H), 8.03 (dd,1H,J=8.0 and 1.9 Hz), 9.2 (bs,1H,OH).

2-(3,5-Dibromo,4-hydroxybenzoyl)-ethyl benzoate (45)

A stirred solution of starting material 44 (6.75 g, 25 mmol) in absolute ethanol (50 mL) was cooled to 0°C and treated dropwise with bromine (2.8 mL, 52 mmol). After all the bromine had been added, the temperature was kept at 0°C and the reaction progress followed by tlc (ethyl acetate-hexane 2:3). After 1 h, the reaction was found to be incomplete so additional bromine (0.4 mL, 7.4 mmol) was added. After stirring for a further 15 min, the solvent was evaporated under reduced pressure to give a red oil. This oil was coevaporated several times with carbon tetrachloride and finally treated with hexane to allow crystallization. The solid was recovered by filtration and washed with the minimum amount of cold absolute ethanol to remove the orange colour. The filtrate was evaporated under reduced pressure and the residue processed as described before (crystallization with hexane, filtration and washing with cold absolute ethanol). A total of 8.37 g (19.6 mmol, 78%) of the desired compound 45 was obtained as a white fluffy solid.

M.p.: 136-137°C; IR($CHCl_3$): 3500, 1720, 1670, 1585, 1545, 1475, 1400, 1290, 1250, 1215, 1160, 1090 and 740 cm^{-1}; ^1H NMR (acetone d-6) δ: 1.13 (t,3H,J=7.0 Hz), 4.13 (q,2H,J=7.0 Hz), 7.48 (dd,1H,J=7.0 and 1.6 Hz), 7.69 (m,2H), 7.83 (s,2H), 8.06 (dd,1H,J=7.0 and 1.6 Hz).

2-(3,5-Dibromo,4-hydroxybenzoyl)-isopropyl benzoate (48)

2-(4-Hydroxybenzoyl)-benzoic acid (43) (8.78 g, 36.3 mmol) was esterified in refluxing isopropanol (80 mL) containing sulfuric acid (4.0 mL) for 32 h. A total of 7.78 g (27.4 mmol, 76%) of 2-(4-hydroxybenzoyl)-isopropyl benzoate was obtained as a white powder.

M.p.: 95-96°C; IR(DMSO): 3450, 1720, 1660, 1610-1585, 1520, 1295-1280, 1250, 1175, 1155, 1110 and 855 cm^{-1}; ^1H NMR (acetone d-6) δ: 1.03 (d,6H,J=6 Hz), 4.92 (m,1H,J=6 Hz), 6.92 and 7.64 (2d, 4H, AA'BB' pattern, J=9 Hz), 7.40 (d,1H,J=7 Hz), 7.60-7.71 (m,2H), 7.99 (d,1H,J=7 Hz), 9.23 (bs,1H,OH).

To a stirred solution of 2-(4-hydroxybenzoyl)-isopropyl benzoate (5.84 g, 20.5 mmol) in ice cold isopropanol (25 mL) was slowly added bromine (2.3 mL, 42 mmol). After all the bromine was added, the reaction temperature was kept at 0°C and progress was followed by tlc (ethyl acetate-hexane 1:9). After 1.5 h, the reaction was still incomplete, so additional bromine (1.0 mL, 18 mmol) was added. After stirring the solution for an extra 15 min, the solvent was evaporated under reduced pressure and the residue placed in a freezer overnight. The precipitate formed was collected by filtration, washed with the minimum amount of cold isopropanol to remove the orange colour and air dried. The filtrate was evaporated under reduced pressure and the residue treated as described above to recover more product. A total of 4.80 g (10.8 mmol, 53%) of the desired compound 48 was obtained as a yellowish solid.

M.p.: 140-144°C; IR(DMSO): 3450, 1715, 1670, 1580, 1545, 1480, 1400-1380, 1160, 1110 and 780 cm^{-1}; ^1H NMR (acetone d-6) δ: 1.12 (d,6H,J=6.6 Hz), 4.98 (m,1H,J=6.6 Hz), 7.47 (d,1H,J=7.0 Hz), 7.72 (m,2H), 7.85 (s,2H), 8.06 (d,1H,J=7.0 Hz).

4.4 PHENOLTRIMELLITEINS

3',3",5',5"-Tetrabromophenoltrimellitein methyl esters 50(a,b)

Using the procedure of Orndorff and his coworkers (22), trimellitic anhydride (51) (1.9 g, 9.89 mmol), anhydrous zinc chloride (4.0 g, 29.3 mmol) and phenol (2.8 g, 29.8 mmol) were mixed together and heated at 150°C. After 2.5 h, the homogenous deep red mixture was poured, while

still hot, into aqueous sodium hydroxide 40% (40 mL) and the solution filtered. The filtrate was acidified with conc. hydrochloric acid until the pH of the solution was acidic to litmus paper and the precipitate which formed was collected by filtration. The precipitate was redissolved in aqueous sodium hydroxide 40% (40 mL), the solution filtered, the filtrate acidified with conc. hydrochloric acid and the precipitate filtered. The precipitate was finally dissolved in ether, dried over anhydrous magnesium sulfate, filtered and the solvent evaporated under reduced pressure to give 3.25 g (9.13 mmol, 92% crude) of phenoltrimelliteins 52(a,b) as a greyish-brown solid (m.p. 154-156°C, lit(22) 155-156°C). The compound was used directly in the next step.

To a solution of the phenoltrimelliteins (52(a,b)) (3.20 g, 8.99 mmol) in absolute methanol (20 mL) was added sulfuric acid (1 mL) and the mixture heated to reflux. The reaction was monitored by tlc (ethyl acetate-hexane 3:2) by following the formation of a new compound at R_f = 0.31. After 2.5 h, the mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The black residue obtained was dissolved in ether, washed several times with water and brine, dried over anhydrous magnesium sulfate, filtered and the solvent evaporated to give 2.15 g of a brownish black solid. The mixture was purified by column chromatography (flash, 5 cm, ethyl acetate-hexane 1:1) and 1.57 g (4.17 mmol, 46%) of the phenoltrimellitein methyl esters (53(a,b)) was collected as a light brown solid.

M.p.: 117-141°C; IR($CHCl_3$): 3600, 3560-3200, 1760, 1730, 1615, 1600, 1520, 1440, 1300, 1180, 930 and 840 cm^{-1}; ^1H NMR (acetone d-6) δ: 3.91 and 3.93 (2s,3H), 6.84 and 7.18 (2dd,8H,AA'BB' pattern, J=8.9 and 1.9 Hz), 7.80-8.41 (m,3H), 8.63 (s,2H,OH).

To a solution of the phenoltrimellitein methyl esters (53(a,b)) (1.0 g, 2.66 mmol) in methanol (10 mL) was slowly added bromine (0.57 mL, 11.17 mmol) at 0°C and under stirring. The reaction was monitored by tlc (ethyl acetate-hexane 2:5) by following the formation of a new compound at R_f =0.46. At the end of the reaction (0.5 h), the mixture was stirred at room temperature for 0.25 h and the solvent evaporated under reduced pressure. The black residue obtained was dissolved in ether, washed several times with water and then with brine, dried over anhydrous magnesium sulfate, filtered and the solvent evaporated to give 1.80 g of a brown solid. This solid was purified by column chromatography (flash, 5 cm, ethyl acetate-hexane 2:5) to give 1.63 g (2.35 mmol, 88%) of 3',3",5',5"-tetrabromophenoltrimellitein methyl esters (50(a,b)) as a brown solid.

M.p.: 103-129°C; IR($CHCl_3$): 3510, 1780, 1735, 1630, 1565, 1480, 1445, 1405, 1330, 1285, 1170, 1125, 1100, 1075, 995, 955 and 875 cm^{-1}; ^1H NMR (acetone d-6) δ: 3.92 and 3.94 (2s,3H), 7.57 and 7.59 (2s,4H), 8.06-8.49 (m,3H), 8.95 (bs,2H,OH).

4.5 TRIPHENYLMETHANE INDICATOR DYES

4.5.1 Preparation of Triphenylmethane Intermediates

The preparation of compound 65 exemplifies the general procedure for the synthesis of all the triphenylmethane intermediates described in this study.

3',3"-Dicarbomethoxy-4',4"-dihydroxy-5',5"-dimethyl triphenylmethane (65)

To a stirred mixture of methyl cresotate (16.0 g, 96.4 mmol) and sulfuric acid (8.4 mL) in benzene (100 mL) at room temperature was added dropwise a solution of benzaldehyde (5.0 g, 47.2 mmol) in benzene (100 mL). As the addition proceeded, an orange-red oil separated from the reaction mixture. The reaction progress was followed by tlc (ethyl acetate-hexane 15:85). After 21 h, the benzene layer was decanted and the oily residue extracted with benzene (3X 200 mL). The benzene extracts were combined, washed several times with water until neutral to litmus paper and then with brine, dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure to give a white solid. The solid was steam distilled to remove any excess of methyl cresotate and benzaldehyde and air dried to give 9.22 g (21.9 mmol, 44%) of compound 65 as a white powder.

Alternatively, after steam distillation, the solid can be dried by extraction with an organic solvent (e.g. chloroform, benzene), treatment of the solution with anhydrous magnesium sulfate, filtration and evaporation of the solvent under reduced pressure.

M.p.: 169-171°C; IR($CHCl_3$): 3300-3100, 1680, 1620, 1480, 1450, 1355, 1300-1275, 1235, 1205, 1135, 1030 and 800 cm^{-1}; ^1H NMR (acetone d-6) δ: 2.20 (s,6H), 3.86 (s,6H), 5.35 (s,1H), 7.07 (s,2H), 7.26 and 7.09 (2m,5H), 7.40 (s,2H) and 10.96 (s,2H,OH).

2,6-Dichloro-3',3"-dicarbomethoxy-4',4"-dihydroxy-5',5"-dimethyl triphenylmethane (66)

The mixture (in the proportions stated for the synthesis of 65 above) was stirred for 48 h and the reaction progress was monitored by tlc (ethyl acetate-hexane 1:1). After isolation of the product, the solid was washed with cold methanol to remove residual starting materials and air dried. The desired compound 66 was obtained in 58% yield as a white solid.

M.p.: 222-224°C; IR($CHCl_3$): 3200, 1675, 1620, 1565, 1480, 1450, 1355, 1300-1280, 1210, 1135 and 740 cm^{-1}; ^1H NMR (acetone d-6) δ: 2.18 (s,6H), 3.87 (s,6H), 6.31 (s,1H), 7.24 (bs,2H), 7.24-7.51 (m,5H).

2,4-Dichloro-3',3"-dicarbomethoxy-4',4"-dihydroxy-5',5"-dimethyl triphenylmethane (67)

The mixture (in the proportions stated for the synthesis of 65 above) was stirred for 24 h and reaction progress followed by tlc (ethyl acetate-hexane 1:9). The desired compound (67) was obtained in 81% yield as a white solid.

M.p.: 207-209°C; IR($CHCl_3$): 3200, 1680, 1620, 1475, 1450, 1360, 1290-1285, 1235, 1205, 1135, 800 and 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.23 (s,6H), 3.89 (s,6H), 5.70 (s,1H), 6.87 (d,1H,J=8.0 Hz), 7.01 (s,2H), 7.19 (d,1H,J=8.0 Hz), 7.33 (s,2H), 7.42 (s,1H), 11.01 (s,2H,OH).

4-Nitro-3',3"-dicarbomethoxy-4',4"-dihydroxy-5',5"-dimethyl triphenylmethane (68)

The mixture (in the proportions stated for the synthesis of 65 above) was stirred for 5 h and reaction progress followed by tlc (ethyl acetate-hexane 15:85). Compound 68 was isolated in 61% yield as a white solid.

M.p.: 203-204°C; IR($CHCl_3$): 3200, 1685, 1620, 1530, 1480, 1450, 1360, 1300, 1280, 1140, 1030 and 860 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.20 (s,6H), 3.86 (s,6H), 5.42 (s,1H), 7.02 (s,2H), 7.24 and 8.14 (2d,4H,AA'BB' pattern, J=8.0 Hz), 7.33 (s,2H), 10.99 (s,2H,OH).

2-Nitro-3',3"-dicarbomethoxy-4',4"-dihydroxy-5',5"-dimethyl triphenylmethane (69)

The mixture (in the proportions stated for the synthesis of 65 above) was stirred for 6 d and reaction progress followed by tlc (ethyl acetate-hexane, 15:85). Compound 69 was obtained in 57% yield as a yellow solid.

M.p.: 174-176°C; IR($CHCl_3$): 3200, 1685, 1620, 1590, 1480, 1450, 1360, 1305-1280, 1140 and 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.21 (s,6H), 3.87 (s,6H), 6.10 (s,1H), 7.01 (s,2H), 7.10 (dd,1H,J=7.4 and 1.5 Hz), 7.37 (s,2H), 7.41 (dt,1H,J=7.6 and 1.5 Hz), 7.53 (dt,1H,J=7.6 and 1.5 Hz), 7.89 (dd,1H,J=7.3 and 1.5 Hz), 11.00 (s,2H,OH).

2-Choro-5-nitro-3',3"-dicarbomethoxy-4',4"-dihydroxy-5',5"-dimethyl triphenylmethane (70)

The mixture (in the proportions stated for the synthesis of 65 above) was stirred for 20 h and reaction progress followed by tlc (ethyl acetate-hexane 15:85). Compound 70 was obtained in 40% yield as a white solid after recrystallization from acetone-water.

M.p.: 201-202°C: IR($CHCl_3$): 3200, 1685, 1620, 1580, 1540, 1480, 1450, 1355, 1295, 1280, 1135, 1050, 1030 and 900 cm^{-1}; ^1H NMR (acetone d-6) δ: 2.17 (s,6H), 3.86 (s,6H), 5.94 (s,1H), 7.26 (d,2H,J=2.0 Hz), 7.45 (s,2H), 7.76 (d,1H,J=8.7 Hz), 7.80 (d,1H,J=2.4 Hz), 8.16 (dd,1H,J=8.7 and 2.4 Hz), 11.05 (s,2H,OH).

4-Cyano-3',3"-dicarbomethoxy-4',4"-dihydroxy-5',5"-dimethyl triphenylmethane (71)

The mixture (in the proportions stated for the synthesis of 65 above) was stirred for 24 h and reaction progress followed by tlc (ethyl acetate-hexane 2:3). Compound 71 was obtained in 51% yield as a white solid.

M.p.: 192-196°C; IR($CHCl_3$): 3200, 2240, 1685, 1620, 1480, 1450, 1390, 1360, 1310-1280, 1140, 1030, 1000, 900 and 860 cm^{-1}: ^1H NMR ($CDCl_3$) δ: 2.21 (s,6H), 3.88 (s,6H), 5.40 (s,1H), 7.02 (d,2H,J=2.3 Hz), 7.19 and 7.60 (2d,4H,AA'BB' pattern, J=2.6 Hz), 7.34 (d,2H,J=2.3 Hz), 11.00 (s,2H,OH).

2,3,5-Trichloro-3',3"-dicarbomethoxy-4',4"-dihydroxy-5',5"-dimethyl triphenylmethane (72)

The mixture (in the proportions stated for the synthesis of 65 above) was stirred for 72 h and reaction progress followed by tlc (ethyl acetate-hexane 1:9). Compound 72 was obtained in 73% yield as a white solid.

M.p.: 189-191°C; IR($CHCl_3$): 3200, 1685, 1620, 1580, 1565, 1480, 1455, 1360, 1305, 1285, 1140, 1030 and 830 cm^{-1}; ^1H NMR (acetone d-6) δ: 2.17 (s,6H), 3.86 (s,6H), 5.88 (s,1H), 6.88 (d,1H,J=2.0 Hz), 7.24 (d,2H,J=2.0 Hz), 7.43 (d,2H,J=2.0 Hz), 7.57 (d,1H,J=2.0 Hz).

2,3,6-Trichloro-3',3"-dicarbomethoxy-4',4"-dihydroxy-5',5"-dimethyl triphenylmethane (73)

The mixture (in the proportions stated for the synthesis of 65 above) was stirred for 72 h and reaction progress followed by tlc (ethyl acetate-hexane 1:9). Compound 73 was obtained in 65% yield as a white solid.

M.p.: 198-200°C; IR($CHCl_3$): 3200, 1680, 1620, 1480, 1450, 1390, 1360, 1305-1280, 1240, 1175, 1140, 1090, 1030 and 815 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.23 (s,6H), 3.88 (s,6H), 6.28 (s,1H), 7.11 (bs,2H), 7.35 (m,2H), 7.44 (d,2H,J=1.0 Hz), 11.01 (s,2H,OH).

2,4,6-Trichloro-3',3"-dicarbomethoxy-4',4"-dihydroxy-5',5"-dimethyl triphenylmethane (74)

Compound 74 was prepared from the condensation of 2,4,6-trichlorobenzaldehyde and methyl cresotate. The 2,4,6-trichlorobenzaldehyde (37) was obtained from the commercially available 2,4,6-trichloroaniline according to the method of Jolad and Rajagopal (38).

A mixture of 2,4,6-trichlorobenzaldehyde and methyl cresotate in benzene containing sulfuric acid (see the synthesis of compound 65 for the proportions) was stirred for 24 h and the reaction progress followed by tlc (ethyl acetate-hexane 1:9). Compound 74 was obtained in 74% yield as a white solid.

M.p.: 203-205°C; IR($CHCl_3$): 3400-2850, 1680, 1615, 1580, 1550, 1480, 1450, 1385, 1355, 1300-1265, 1135, 1030 and 860 cm^{-1}; ^1H NMR (acetone d-6) δ: 2.18 (s,6H), 3.87 (s,6H), 6.27 (s,1H), 7.25 (s,2H), 7.35 (s,1H), 7.48 (s,2H), 7.57 (s,1H), 11.04 (s,2H).

2,6-Dichloro-3',3"-dicarbomethoxy-4',4"-dihydroxy-5',5"-dichloro triphenylmethane (75)

3-Chlorosalicylic acid methyl ester 78 was prepared from esterification (H_2SO_4/MeOH, Δ, 72 h, 92% yield) of commercially available 3-chlorosalicylic acid. The ester 78 was purified by distillation (90-92°C/0.2 mm Hg, mp. 31-33°C) prior to use.

A mixture of ester 78 and 2,6-dichlorobenzaldehyde (77) in benzene containing sulfuric acid (in the proportions stated for the synthesis of 65 above) was stirred for 96 h and reaction progress followed by tlc (ethyl acetate-hexane 1:9). Compound 75 was obtained in 15% yield as a white solid.

M.p.: 168-170°C; IR($CHCl_3$): 3300-2900, 1685, 1610, 1565, 1500, 1450, 1340, 1290, 1265, 1180, 1110, 995, 950, 810 and 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.92 (s,6H), 6.40 (s,1H), 7.17-7.64 (m,5H), 7.64 (s,1H), 11.31 (s,2H,OH).

2,6-Dichloro-3',3"-dicarbomethoxy-4',4"-dihydroxy triphenylmethane (81)

2,6-Dichlorobenzaldehyde 77 (25.25 g, 150 mmol) was added in one to two gram portions to sulfuric acid (153 mL) precooled at 10°C. When the aldehyde was completely dissolved, salicylic acid (79) (46.27 g, 335 mmol) was added rapidly. The mixture was slowly warmed to room temperature and stirred for 90 h. The mixture was then poured slowly into 1L of ice water,

the flocculent precipitate allowed to settle, and the supernatant removed by suction. The precipitate was dissolved in ethyl acetate (500 mL), the organic phase washed several times with water (until the washings were neutral to litmus paper) and then with brine, dried over anhydrous magnesium sulfate, filtered and the solvent evaporated to give the crude diacid 80 as a light brown solid. This material was used directly for the next step.

To a solution of the crude diacid 80 in absolute methanol (100 mL) was added sulfuric acid (10 mL) and the mixture heated under reflux. During the reaction, a white solid precipitated out of the mixture. After 40 h, the mixture was cooled to room temperature, the solid formed was collected by filtration, washed with ice cold absolute methanol and air dried. The desired compound 81 was obtained as a white solid (8.24 g, 19.5 mmol, 13%).

M.p.: 181-183°C; IR($CHCl_3$): 3220, 1685, 1620, 1600, 1570, 1500, 1450, 1350-1320, 1310, 1300, 1275, 1095, 980 and 850 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.88 (s,6H), 6.30 (s,1H), 6.92 (d,2H,J=8.5 Hz), 7.12-7.31 (m,3H), 7.34 (dd, 2H, J=8.5 and 2.2 Hz), 7.62 (d,2H,J=2.2 Hz), 10.74 (s,2H,OH); ^{13}C NMR ($CDCl_3$) δ: 50.429, 52.274, 112.064, 117.512, 128.783, 129.766, 130.045, 130.895, 136.391, 136.512, 138.017, 160.268 and 170.472.

2,6-Dichloro-3',3"-dicarbomethoxy-4',4"-dihydroxy-5',5"-dibromo triphenylmethane (76)

To a stirring suspension of compound 81 (8.22 g, 18.29 mmol) in absolute methanol (100 mL) was added a solution of bromine (3.29 mL, 45.72 mmol) in methanol (40 mL) at room temperature. The mixture was then diluted with chloroform until all the starting material became soluble (approx. 200 mL of chloroform was used). The reaction progress was then followed by tlc (ethyl acetate-hexane 1:5). After 2 h, the solvent was evaporated under reduced pressure, the resulting orange solid was collected by filtration, and this was washed with the minimum amount of cold methanol to remove excess bromine. The yellowish solid was air dried to give 11.05 g (17.32 mmol, 95%) of the desired compound 76 as a single isomer.

M.p.: 242-244°C; IR($CHCl_3$): 3400-2900, 1690, 1620, 1450, 1340, 1290, 1260 and 1180 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.91 (s,6H), 6.25 (s,1H), 7.20-7.40 (m,3H), 7.52 (d,2H,J=2.3 Hz), 7.59 (d,2H,J=2.3 Hz), 11.45 (s,2H,OH); ^{13}C NMR ($CDCl_3$) δ: 49.869, 52.844, 111.349, 113.168, 129.366, 129.960, 131.441, 136.245, 136.791, 139.230, 156.980, 169.987.

4.5.2 Triphenylmethane Indicator Dyes

5[(3-carbomethoxy-5-methyl-4-oxo-2,5-cyclohexadiene-1-ylidene)(2,6-dichlorophenyl)methyl]-2-hydroxy-3-methyl, methyl benzoate (60)

To a solution of starting material 66 (1.0 g, 2.05 mmol) in benzene (20 mL) was added freshly prepared silver oxide[a] (2.33 g, 10.25 mmol) and the mixture was then heated to reflux. The reaction progress was monitored by tlc (ethyl acetate-hexane 1:5) by following the formation of the compound at R_f = 0.11 which turned deep blue upon contact with a drop of V simulant. After 72 h, the mixture was cooled to room temperature and filtered on celite to remove the silver salts. The filtrate was evaporated under reduced pressure and the residue purified by column chromatography (flash, 3 cm, ethyl acetate-hexane 2:3) to give 0.398 g (0.819 mmol, 40%) of the desired compound 60 (orange solid) as a mixture of two isomers.

M.p.: 205-208°C; IR($CHCl_3$): 3300-2900, 1740, 1680, 1640, 1610, 1530, 1450, 1435, 1365, 1335, 1290, 1215, 1135, 1040 and 740 cm^{-1}; ^1H NMR (acetone d-6) δ: 1.90 and 2.00 (2d,3H,CH_3,J=1.3 Hz), 2.25 (s,3H,CH_3), 3.69 and 3.75 (2s,3H,COOMe), 3.95 (s,3H,COOMe), 6.82 (m,1H), 7.45 (m,1H), 7.60 (m,3H), 7.76 (m,1H), 8.00 (m,1H), 11.40 (s,2H,OH).

2,6-Dichloro-3',3"-dicarbomethoxy-4',4"-dihydroxy-5',5"-dimethyl triphenylcarbinol (82)

To a stirred solution of compound 66 (0.488 g, 1 mmol) in sulfuric acid (3 mL) was slowly added sodium nitrite (0.077 g, 1.12 mmol) at 0°C. After the addition, the mixture was slowly warmed to room temperature and reaction progress followed by tlc (ethyl acetate-hexane 3:7). After 20 h, the mixture was poured into ice cold water (20 mL) and this was extracted with methylene chloride (2 x 20 mL). The organic extracts were combined, dried over anhydrous magnesium sulfate, and filtered. The solvent was evaporated under reduced pressure to give 0.298 g (0.61 mmol, 61%) of carbinol 82 as a red solid. The product (R_f = 0.17) had the following characteristics:

M.p.: 104-107°C; IR($CHCL_3$)[b]: 3300-2900, 1740, 1685, 1640, 1530, 1450, 1440, 1365, 1355-1345, 1290, 1250, 1220, 1205, 1135, 1040, 800 and 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.10 (s,6H), 3.83 (s,6H), 7.33 (bs,2H), 7.57-7.70 (m,6H).

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[a] Silver oxide was freshly prepared from silver nitrate (1 g) and sodium hydroxide (1 g) in water. The oxide, which precipitate in the reaction mixture, was filtered, washed successively with water and acetone and dried under vacuum (100°C/15 mm Hg, 8 h).

[b] The infrared spectrum shows a band at 1740 cm^{-1} which could correspond to the ester function of the oxidized material 60. Although the infrared spectrum might suggest the presence of some indicator dye 60, this compound was present in too low a quantity to be seen in the ^1H NMR spectrum.

3',3"-dicarbomethoxy-4',4"-dihydroxy-5',5"-dimethyl triphenylcarbinol (93)

To a solution of starting material 65 (0.5 g, 1.17 mmol) in chloroform (20 mL) was added silver oxide (1.62 g, 7.02 mmol) and the mixture heated under reflux. After 20 h, tlc analysis (ethyl acetate-hexane 3:7) showed the formation of a new compound (R_f = 0.11) which turned deep blue with V simulant. After 48 h, the mixture was cooled to room temperature and filtered on celite to remove the silver salts. The filtrate was evaporated under reduced pressure to leave a red solid (0.505 g, 1.14 mmol, 98% yield) having no indicator properties. The analysis showed the presence of a major compound (R_f = 0.38 instead of 0.11) which was identified as the carbinol 93.

M.p.: 155-158°C; IR($CHCl_3$): 1680, 1620, 1475, 1450, 1355, 1290, 1240, 1215, 1130 and 800 cm^{-1}; ^1H NMR (acetone d-6) δ: 2.16 (s,6H), 3.86 (s,6H), 5.37 (s,1H,OH*), 7.32 (m,7H), 7.70 (m,2H), 11.06 (s,2H,OH*).

5-[(3-Carbomethoxy-5-methyl-4-oxo-2,5-cyclohexadiene-1-ylidene) (2,4-dichlorophenyl)methyl]-2-hydroxy-3-methyl, methyl benzoate (83)

To a solution of 67 (0.3 g, 0.61 mmol) in chloroform (10 mL) was added silver oxide (0.85 g, 3.67 mmol) and the mixture was then heated to reflux. After 20 h, the mixture was cooled to room temperature, filtered on celite to remove the silver salts and the filtrate evaporated under reduced pressure to give 0.298 g (0.61 mmol, ~100%) of compound 83 (mixture of 2 isomers) as an orange solid. The compound could not be purified by column chromatography because of its instability on silica gel but was sufficiently pure to permit its characterization.

M.p.: 145-180°C; IR($CHCl_3$): 3300-2800, 1730, 1680, 1635-1600, 1590, 1525, 1475, 1445, 1385, 1355, 1290, 1180, 1130 and 1035 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.02 and 2.09 (2s,3H,CH_3), 2.30 (s,3H,CH_3), 3.87 and 3.89 (2s,2H,COOMe), 3.98 (s,3H,COOMe), 6.80 (s,1H), 7.16-7.63 (m,5H), 8.00 (s,1H), 11.45 (s,2H,OH).

4-Nitro-3',3"-dicarbomethoxy-4'-4"-dihydroxy-5',5"-dimethyl triphenylcarbinol (94)

To a solution of starting material 68 (0.3 g, 0.64 mmol) in chloroform (20 mL) was added silver oxide (0.89 g, 3.87 mmol) and the mixture was then heated under reflux for 25 h. The mixture was cooled to room temperature, filtered on celite to remove the silver salts and the solvent was evaporated under reduced pressure to give 0.300 g (0.64 mmol, ~100% crude) of a red solid. This solid was analyzed by ^1H NMR and proved

* Signals exchangeable with D_2O.

to be the desired indicator dye 84.

Compound 84 (mixture of 2 isomers): ^{1}H NMR ($CDCl_3$) δ: 2.02 and 2.06 (2s,3H,CH_3), 2.28 (s,3H,CH_3), 3.83 and 3.85 (2s,3H,$COOCH_3$), 3.94 (s,3H,$COOCH_3$), 7.00-8.35 (m,8H), 11.46 (s,1H,OH).

Compound 84 was nevertheless very unstable and was transformed to the carbinol 94 during the following work up. The solid isolated was dissolved in ethyl acetate, diluted with water and treated with acetic acid. The two phases were separated, the organic layer washed with water and then with brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated to give an orange solid which was identified as pure 94.

Carbinol 94

M.p.: 95-97°C; IR($CHCl_3$): 3350-2850, 1680, 1615, 1530, 1475, 1450, 1390, 1355, 1295, 1270, 1230, 1135, 1020, 930, 900, 865 and 845 cm^{-1}; ^{1}H NMR (acetone d-6) δ: 2.16 (s,6H), 3.87 (s,6H), 5.76 (s,1H,OH*), 7.36 (s,2H), 7.69 (s,2H), 7.65 and 8.19 (2d,4H,AA'BB' pattern, J=9 Hz), 11.08 (s,2H,OH*).

4-Cyano-3',3"-dicarbomethoxy-4',4"-dihydroxy-5',5"-dimethyl triphenylcarbinol (91)

To a solution of starting material 71 (0.5 g, 1.12 mmol) in chloroform (20 mL) was added silver oxide (1.55 g, 6.74 mmol) and the mixture was then heated under reflux for 72 h. The reaction mixture was cooled to room temperature, filtered on celite to remove the silver salts and the solvent was evaporated under reduced pressure to give 0.671 g of a yellow solid having no indicator properties. The crude compound was purified by column chromatography (flash, 3 cm, ethyl acetate-hexane 3:7) to give 0.410 g (0.918 mmol, 82%) of the carbinol 91 as a yellow solid.

M.p.: 204-207°C; IR($CHCl_3$): 3610, 3300-2820, 2230, 1680, 1610, 1475, 1450, 1385, 1355, 1290, 1270, 1135, 1020, 990, 930, 900 and 850 cm^{-1}; ^{1}H NMR (acetone d-6) δ: 2.16 (s,6H,CH_3), 3.87 (s,6H,$COOCH_3$), 5.70 (s,1H,OH*), 7.34 (s,2H), 7.66 (s,2H), 7.57 and 7.73 (2d,4H,AA'BB' pattern, J=8.6 Hz), 11.07 (s,2H,OH*).

* Signals exchangeable with D_2O.

5-[(3-Carbomethoxy-5-methyl-4-oxo-2,5-cyclohexadiene-1-ylidene)(2-chloro-5-nitrophenyl)methyl]-2-hydroxy-3-methyl, methyl benzoate (85)

To a solution of 70 (0.5 g, 1.00 mmol) in chloroform (20 mL) was added silver oxide (1.38 g, 6.00 mmol) and the mixture was then heated under reflux for 90 h. The reaction mixture was cooled to room temperature, filtered on celite to remove the silver salts and the solvent was evaporated under reduced pressure to give 0.64 g (>100%) of compound 85 (mixture of isomers) as an orange solid. The compound was not purified.

M.p.: 175-185°C; IR($CHCl_3$): 1740, 1690, 1640, 1615, 1540, 1470, 1450, 1355, 1280, 1140 and 1040 cm^{-1}; ^1H NMR (acetone d-6) δ: 1.88 and 1.99 (2s,3H,CH_3), 2.23 (s,3H,CH_3), 3.66 and 3.74 (2s,3H,COOMe), 3.94 (s,3H,COOMe), 7.00-8.40 (m,7H), 11.40 (s,2H,OH).

5-[(3-Carbomethoxy-5-methyl-4-oxo-2,5-cyclohexadiene-1-ylidene)(2,3,5-trichlorophenyl)methyl]-2-hydroxy-3-methyl, methyl benzoate (86)

To a solution of 72 (1.0 g, 1.91 mmol) in benzene (40 mL) was added silver oxide (2.20 g, 9.58 mmol) and the mixture was then heated under reflux for a period of 72 h. The mixture was cooled to room temperature, filtered on celite to remove the silver salts and the solvent was evaporated under reduced pressure to give 1.17 g of an orange solid. The crude material was purified by column chromatography (flash, 3 cm, ethyl acetate-hexane 2:5) to give 0.70 g (1.351 mmol, 71%) of compound 86 as a mixture of isomers.

M.p.: 115-175°C; IR($CHCl_3$): 3300-2900, 1730, 1680, 1635, 1605, 1525, 1470, 1445, 1410, 1390, 1360, 1340, 1290-1270, 1230-1205, 1135 and 1035 cm^{-1}; ^1H NMR (acetone d-6) δ: 1.90 and 1.98 (2s,3H,CH_3), 2.24 (s,3H,CH_3), 3.69 and 3.76 (2s,3H,COOMe), 3.95 (s,3H,COOMe), 7.0-8.0 (m,6H), 11.43 (s,1H,OH).

5-[(3-Carbomethoxy-5-methyl-4-oxo-2,5-cyclohexadiene-1-ylidene)(2,3,6-trichlorophenyl)methyl]-2-hydroxy-3-methyl, methyl benzoate (87)

To a solution of 73 (1.0 g, 1.91 mmol) in benzene (40 mL) was added silver oxide (2.20 g, 9.58 mmol) and the mixture was heated under reflux for a period of 5 d. The mixture was then cooled to room temperature, filtered on celite to remove the silver salts and the solvent was evaporated under reduced pressure to give 1.08 g of an orange solid. The crude product was purified by column chromatography (flash, 3 cm, ethyl acetate-hexane 2:5) to give compound 87 as an orange solid (0.74 g, 1.428 mmol, 75% yield).

M.p.: 80-97°C; IR($CHCl_3$): 3300-2850, 1735, 1685, 1640, 1610, 1530, 1475, 1450, 1440, 1390, 1360, 1340, 1285, 1250, 1230, 1210, 1180, 1145 and 1035 cm^{-1}; ^1H NMR (acetone d-6) δ: 1.90 and 2.00 (2s,3H,CH_3), 2.25 (s,3H,CH_3), 3.68 and 3.75 (2s,3H,COOMe), 3.96 (s,3H,COOMe), 6.90 (m,1H), 7.30-7.99 (m,5H), 11.42 (s,1H,OH).

5-[(3-Carbomethoxy-5-methyl-4-oxo-2,5-cyclohexadiene-1-ylidene)(2,4,6-trichlorophenyl)methyl]-2-hydroxy-3-methyl, methyl benzoate (88)

To a solution 74 (0.5 g, 0.955 mmol) in benzene (20 mL) was added silver oxide (1.09 g, 4.77 mmol) and the mixture was then heated under reflux for a period of 72 h. The mixture was then cooled to room temperature, filtered on celite to remove the silver salts and the solvent was evaporated under reduced pressure to give 0.643 g of an orange solid containing the desired compound 88. Purification by column chromatography (flash, 3 cm, ethyl acetate-hexane 3:7) gave 0.329 g (0.635 mmol, 66%) of compound 88 as an orange solid.

M.p.: 214-217°C; IR($CHCl_3$): 3300-2850, 1735, 1680, 1635, 1605, 1580, 1540, 1475, 1445, 1370, 1340, 1285, 1250, 1140, 1130, 1030 and 865 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.98 and 2.06 (2d,3H,CH_3, J=1.3 Hz), 2.26 (s,3H,CH_3), 3.83 and 3.85 (2s,3H,COOMe), 3.95 (s,3H,COOMe), 6.62 (m,1H), 7.20 (m,1H), 7.35 (m,1H), 7.47 and 7.48 (2s,2H), 7.66 and 7.69 (2d,1H,J=2.1 Hz), 8.02 (d,1H,J=2.9 Hz), 11.40 (s,1H,OH).

5-[(5-Bromo-3-carbomethoxy-4-oxo-2,5-cyclohexadiene-1-ylidene)(2,6-dichlorophenyl)methyl]-3-bromo-2-hydroxy, methyl benzoate (90)

To a solution of 76 (8.0 g, 12.54 mmol) in benzene (400 mL) was added lead tetraacetate (6.68 g, 15.05 mmol) and the mixture was heated under reflux. As the oxidizing agent was added, the mixture turned brownish black and changed further to orange as the reflux temperature was reached. After 1 h, tlc analysis (ethyl acetate-hexane 1:5) showed that the reaction was not complete. More lead tetraacetate (3.5 g, 7.89 mmol) was added and the mixture refluxed for an additional hour. It was then cooled to room temperature and filtered to remove the lead diacetate formed. The filtrate was evaporated under reduced pressure and the solid obtained diluted in ethyl acetate. The organic phase was washed successively with water, then with aqueous hydrochloric acid (10%) and with brine, dried over anhydrous magnesium sulfate, filtered and the solvent was evaporated to give an orange residue. The residue was treated with methanol to allow crystallization and the solid was filtered and air dried to give 7.34 g (11.54 mmol, 92%) of impure 90 as an orange solid. Attempted purification by column chromatography failed so the product was used as obtained.

M.p.: 178-195°C; IR($CHCl_3$): 1740, 1690, 1655, 1445, 1330 and 1010 cm^{-1};

N.B.: Although the crude compound had very good indicator properties with V simulant, the ^1H NMR spectrum showed broad signals between 3.6-4.0 ppm (OMe) and 7.2-8.0 ppm which could not be interpreted.

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