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THIN-LAYER CHROMATOGRAPHIC STUDY ON THE STABILITY OF SOME 2-ARYL-1,3-INDANDIONES ON EXPOSURE TO AIR

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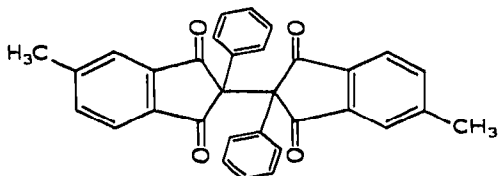
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SUMMARY

The stability of three indandiones, 2-phenyl-1,3-indandione, 2-(2,6-xylyl)-1,3-indandione and 2-mesityl-1,3-indandione, when exposed to air on a silica gel thin layer, was investigated. The stability of a fourth indandione, 2-(3,5-di-*tert.*-butylphenyl)-1,3-indandione, on silica gel and in solution in absolute ethanol and benzene was studied. The indandiones appeared to undergo conversion during the chromatographic procedure. Conversion was fastest with 2-phenyl-1,3-indandione and 2-(3,5-di-*tert.*-butylphenyl)-1,3-indandione, the former being converted into 3-phenyl-4-hydroxyisocoumarin, *o*-(phenylglyoxyloyl)benzoic acid and 2,2'-diphenyl-[2,2'-biindan]-1,1',3,3'-tetrone and the latter into the hydroxyisocoumarin and biindantetrone. In solution also, the conversion products of the 2-(3,5-di-*tert.*-butylphenyl)-1,3-indandione were the hydroxyisocoumarin and biindantetrone derivatives. On silica gel the conversion into the hydroxyisocoumarin was fastest, whereas the main reaction product in solution was the biindantetrone. The conversion rate was higher in benzene (apolar medium) than in ethanol (polar medium).

INTRODUCTION

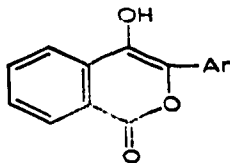
2-Aryl-1,3-indandiones have been reported to be unstable when exposed to air. In 1896, Blank¹ found that on boiling an ethanolic solution of 5-methyl-2-phenyl-1,3-indandione, a biindantetrone ("dimer")* was formed:



2,2'-diphenyl-5,5'-dimethyl-[2,2'-biindan]-1,1',3,3'-tetrone

* In fact, a dehydro-dimer is formed.

A similar "dimerization" was noted by Klosa² and Rigaudy and Aubrun³ when solutions of 2-phenyl-1,3-indandione in ethanol and diethyl ether were exposed to air. Klosa concluded that the "dimer" had been formed in a photochemical reaction, while Rigaudy and Aubrun suggested that a radical mechanism was responsible for the "dimerization". Klosa also noted that during the synthesis and purification of 2-phenyl-1,3-indandione, "dimerization" could be avoided by the use of a nitrogen atmosphere. A further route by which the oxidation of arylindandiones may proceed and which has been studied particularly by Zalukaev and Belyaev^{4,5} is the production of hydroxyisocoumarin (lactone formation):



3-aryl-4-hydroxyisocoumarin

A more extensive review of the instability of arylindandiones in air was published by Moiseev and Poluktov⁶.

This work formed part of a project on the medicinal chemistry of 1,3-indandiones, started by Bruynes⁷ in 1968. A discussion of the synthesis and physicochemical and biological properties of a number of 2-(alkylphenyl)-1,3-indandiones may be found in his Ph.D. thesis⁷. The test compounds selected for our work included 2-phenyl-1,3-indandione (I), 2-(2,6-xylyl)-1,3-indandione (II), 2-mesityl-1,3-indandione (III) and 2-(3,5-di-*tert.*-butylphenyl)-1,3-indandione (IV).

EXPERIMENTAL

Indandiones and conversion products

2-Phenyl-1,3-indandione (m.p. 148–150°)*, 2-(2,6-xylyl)-1,3-indandione (m.p. 164–165°), 2-mesityl-1,3-indandione (m.p. 222–222.5°) and (unlabelled) 2-(3,5-di-*tert.*-butylphenyl)-1,3-indandione (m.p. 134–135°) came from the laboratory stock.

The synthesis of 2-(3,5-di-*tert.*-butylphenyl)-1,3-[di-¹⁴C]indandione was accomplished in two steps^{**}: (a) preparation of [di-¹⁴C]phthalide and (b) its reaction with 3,5-di-*tert.*-butylbenzaldehyde. The phthalide was synthesized as described by Brewster *et al.*⁸ from a mixture of 853 mg (5.1 mmole) of phthalic acid and 147 mg (0.9 mmole) of [di-¹⁴C]phthalic acid (10 mCi)^{***}. The final yield was 668 mg of a crystalline product, m.p. 72–73° (lit.⁸, 72.5–73.5°). Step (b) was based on the modification of Dieckmann's method⁹ by Shapiro and co-workers^{10,11}. The starting materials were 668 mg (4.98 mmole) of [di-¹⁴C]phthalide and 1.1 g (4.6 mmole) of 3,5-di-*tert.*-butylbenzaldehyde, dissolved in 3 ml of methyl propionate. Labelled

* All melting points are uncorrected.

** The reactions were performed by W. F. J. Klopper at the Gist-Brocades N.V. Research Laboratories under the supervision of W. den Besten and J. de Vries.

*** Supplied by The Radiochemical Centre, Amersham, Great Britain.

indandione was obtained in 36% yield (603 mg), m.p. 133–134° [from 1:4 cyclohexane–light petroleum (b.p. 40–60°)], specific activity 5.9 mCi/g. From this batch of high specific activity, a batch with low specific activity (1.0 mCi/g) was prepared.

3-Phenyl-4-hydroxyisocoumarin (V) was obtained in 10% yield, as outlined by Zalukaev and Belyaev⁵, but air instead of oxygen was passed through the mixture for oxidation. Crystallization from 70% acetic acid gave the desired product, m.p. 103–105° (lit.⁵, 104–105°), $\delta(\text{CDCl}_3)$ 3.53 (OH), 7.96 (isocoumarin protons) and 7.30 (phenyl protons), m/e 238.0627 (M^+ , $\text{C}_{15}\text{H}_{10}\text{O}_3$ requires 238.0639) (76%) and other significant peaks at m/e 221 (8%), 210 (12%), 181 (20%), 165 (6%), 152 (11%), 133 (11%), 132 (16%), 105 (base peak) and 77 (49%).

o-(Phenylglyoxyloyl)benzoic acid (VI) was obtained together with the above compound in 18.5% yield. Crystallization from 70% acetic acid afforded the benzoic acid, m.p. 141–144° (lit.⁵, 142°), $\delta(\text{CDCl}_3)$ 6.55 (–COOH)(23)*, and 7.28–8.13 (4H and 5H)(189)*, m/e 254.0580 (M^+ , $\text{C}_{15}\text{H}_{10}\text{O}_4$ requires 254.0579)(0.2%), with other small peaks at m/e 237 (0.6%), 210 (0.8%), 209 (1.2%) and 181 (1.2%) and strong peaks at 149 (base peak), 105 (70%) and 77 (41%).

2,2'-Diphenyl-[2,2'-biindan]-1,1',3,3'-tetrone (VII) was synthesized as described for 2,2'-bis-(3,5-di-*tert.*-butylphenyl)-[2,2'-biindan]-1,1',3,3'-tetrone (IX). M.p. 207–209.5° (lit.¹², 213–214°), $\delta(\text{CDCl}_3)$ 7.80 (indane protons) and 7.24 (phenyl protons), m/e 442.1217 (M^+ , $\text{C}_{30}\text{H}_{18}\text{O}_4$ requires 442.1205) (12%) and other strong peaks at m/e 222 (base peak), 221 (66%), 194 (17%), 193 (15%), 165 (69%), 152 (10%), 105 (20%) and 77 (25%).

For 3-(3,5-di-*tert.*-butylphenyl)-4-hydroxyisocoumarin (VIII), a solution of 20 g of 2-(3,5-di-*tert.*-butylphenyl)-1,3-indandione (IV) in a mixture of 125 ml of methanol and 125 ml of acetone was sprayed on three silica gel 60 F₂₅₄ pre-coated TLC plates, 20 × 40 cm, layer thickness 2 mm (E. Merck, Darmstadt, G.F.R.). The plates were exposed to air for 3 days. Next, the silica gel was removed and extracted with acetone and the extract was subjected to the same procedure. Evaporation of the final solution gave a residue of about 15 g, which was boiled in a mixture of 50 ml of diethyl ether and 50 ml of light petroleum (b.p. 40–60°) and filtered. The filtrate was diluted with 150 ml of light petroleum (b.p. 40–60°) and cooled. The product crystallized and was re-crystallized from a diethyl ether–light petroleum mixture to give the hydroxyisocoumarin (5.5 g, 27%), m.p. 153.5°, m/e 350.1890 (M^+ , $\text{C}_{23}\text{H}_{26}\text{O}_3$ requires 350.1882). For more analytical data, see *Identification* p. 122.

For 2,2'-bis(3,5-di-*tert.*-butylphenyl)-[2,2'-biindan]-1,1',3,3'-tetrone (IX), 350 mg of IV were dissolved in 50 ml of absolute ethanol. The solution became orange-red, and was exposed to air for 1 month, during which period crystals were formed and the orange-red colour began to fade. The crystals (83 mg) were identified as the biindantetrone, m.p. 313.5–315.5°, m/e 666.3875 (M^+ , $\text{C}_{46}\text{H}_{50}\text{O}_4$ requires 666.3865). For more analytical data, see *Identification* p. 122.

Thin-layer chromatography (TLC)

Plates. The following plates were used: (A) silica gel F₂₅₄ pre-coated (fast running) TLC plates, 20 × 20 cm, layer thickness 0.25 mm (E. Merck); (B) silica gel F₁₅₀₀LS₂₅₄ TLC-ready plastic sheets, 20 × 20 cm (Schleicher & Schüll, Dassel,

* Integrated absorption.

G.F.R.); (C) glass plates (10 × 20 cm) were covered with a mixture of 30 g of silica gel GF₂₅₄ "nach Stahl" (E. Merck) in 55 ml of distilled water using a Desaga apparatus. The silica gel had been pre-treated by 24-h extraction with methanol in a Soxhlet apparatus. The plates were dried first in air and then heated at 110–120° in a drying oven. The plates were not re-activated before use.

Eluents. The eluents used were (a) toluene–cyclohexane–ethyl acetate (64:29:7) and (b) chloroform–methanol (97:3).

Procedure. In most instances, samples taken from solutions in absolute ethanol containing 4 mg/ml of indandione were applied to the plates. Conversion of IV in solution on exposure to air was monitored by using solutions of the ¹⁴C-labelled compound (specific activity 1.0 mCi/g) in absolute ethanol and benzene, both also containing 4 mg/ml of indandione. In the latter case, 5- μ l samples were taken from the solutions at regular intervals and applied to the plates in a nitrogen atmosphere. Following elution, the extent of conversion was established by determining the distribution of radioactivity over the various spots.

Detection. The coloured indandione spots were localized directly (I and IV appeared as orange spots and II and III as yellow spots). A one-dimensional Berthold thin-layer scanner was used for the detection of radioactivity and for the determination of the distribution of radioactivity over the various spots.

Identification of conversion products

The analysis was based on nuclear magnetic resonance (NMR) spectroscopic, mass spectrometric and infrared (IR) spectroscopic data. NMR spectra were run in CDCl₃ with TMS as internal standard using a Varian A-60 spectrometer at about 38°. Mass spectra were run on either an AEI MS902 or a Varian-Mat CH5 spectrometer. IR spectra were obtained on a Perkin-Elmer Model 257 spectrophotometer.

RESULTS AND DISCUSSION

Behaviour on thin-layer plates

2-Phenyl-1,3-indandione (I) and 2-(3,5-di-*tert.*-butylphenyl)-1,3-indandione (IV) gave the chromatographic patterns on the left-hand side of Figs. 1 and 2, respectively, on application of freshly prepared ethanolic solutions to (A) plates using eluent (a). Special attention should be paid to the three-spot pattern: *a*, *b* and (weak) *c*. Often, there was a fourth, scarcely observable spot at the starting point. It is remarkable that under identical conditions, 2-(2,6-xylyl)-1,3-indandione (II) and 2-mesityl-1,3-indandione (III) produced only one spot. When elution was delayed until 24 h after exposure to air, not only the original spots of II and III but also other spots were found (see Fig. 3).

The spot patterns thus obtained were, however, different from those of I and IV. Chromatograms with more than one spot after application of a single compound were also obtained by Pomazańska-Kołodziejska¹³ in a study on β -diketones such as phenylindandione and *p*-methoxyphenylindandione. However, she did not identify all compounds responsible for the occurrence of spots.

At first sight, it could be suggested that patterns such as those illustrated here might be due to contaminants. This was, however, not the case in the present study, as shown by the chromatograms obtained with I and IV applied in a nitrogen atmos-

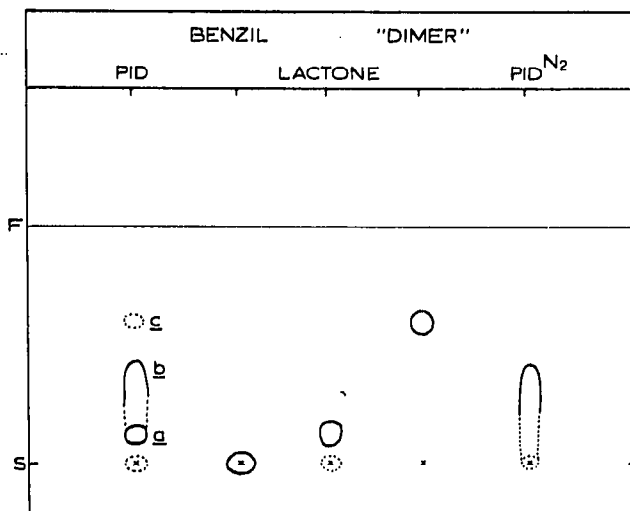


Fig. 1. Chromatographic analysis of 2-phenyl-1,3-indandione (PID) using an (A) plate and eluent (a); see Experimental. PID = Indandione, applied on exposure to air, and eluted 30 min later; PID^{N_2} = indandione, applied in a nitrogen atmosphere; BENZIL = *o*-(phenylglyoxyloyl)benzoic acid; F = front; S = start.

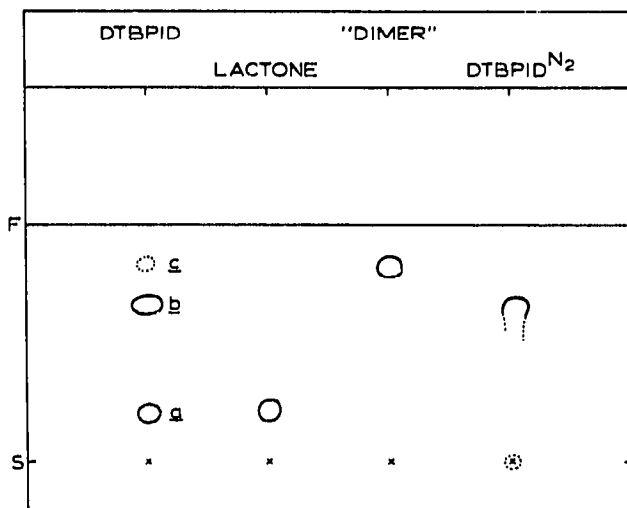


Fig. 2. Chromatographic analysis of 2-(3,5-di-*tert*-butylphenyl)-1,3-indandione (DTBPID) using an (A) plate and eluent (a). DTBPID = indandione, applied on exposure to air, and eluted 30 min later; $\text{DTBPID}^{\text{N}_2}$ = indandione, applied in a nitrogen atmosphere; F = front; S = start.

phere (only one spot was obtained, see the right-hand sides of Figs. 1 and 2). A similar result can be seen for IV in Fig. 4, together with the scans. From these observations, it can only be concluded that after application, conversion of the compounds occurred.

As regards the application in a nitrogen atmosphere, the following should be noted. Daenens and Van Boven¹⁴ have ascertained whether TLC would be a useful

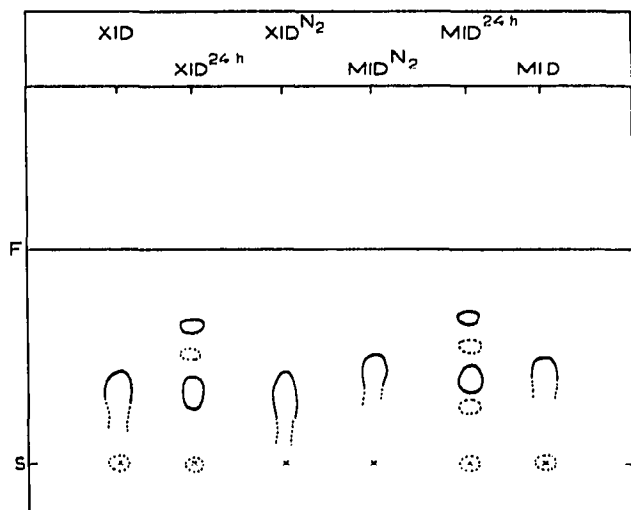


Fig. 3. Chromatographic analysis of 2-(2,6-xylyl)-1,3-indandione (XID) and 2-mesityl-1,3-indandione (MID) using an (A) plate and eluent (a). XID, MID = indandiones, applied on exposure to air, and eluted 30 min later; XID^{24 h}, MID^{24 h} = indandiones, applied on exposure to air, and eluted 24 h later; XID^{N₂}, MID^{N₂} = indandiones, applied in a nitrogen atmosphere; F = front; S = start.

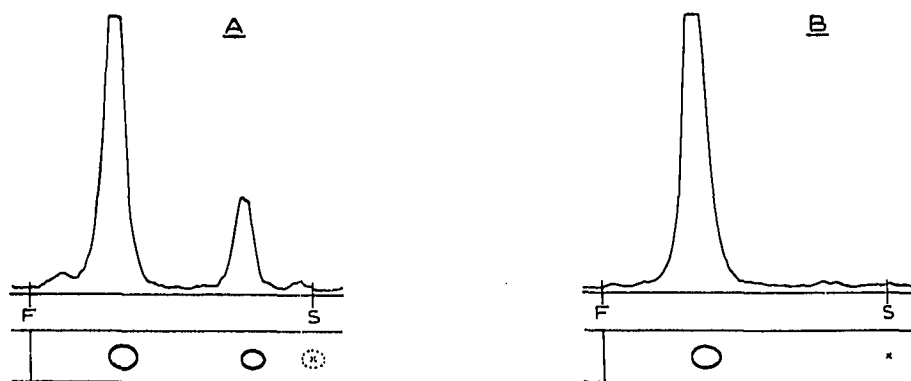


Fig. 4. A, Chromatogram and scan for 2-(3,5-di-*tert.*-butylphenyl)-1,3-[di-¹⁴C]indandione, obtained on an (A) plate following elution with solvent (a). Indandione applied on exposure to air, and eluted 30 min later. B, As in A, but indandione applied in a nitrogen atmosphere. F = front; S = start.

method for determining the purity of some coumarins and arylindandiones such as phenylindandione and *p*-bromo- and *p*-chlorophenylindandione, using silica gel as the carrier and a mixture of chloroform and methanol (97:3) as the eluent. On inspection of their results, it can be seen that, although the indandiones had not been applied to the plates in a nitrogen atmosphere, only the R_F values of the unconverted products are given, and that no information about oxidation, if any, is given. Part of their study was reproduced in our work, showing other spots besides those of indandiones (see Fig. 5).

Identification

The compounds responsible for the various spots were subjected to mass spectrometry and NMR and IR spectroscopy. First, the mass spectra of residues of

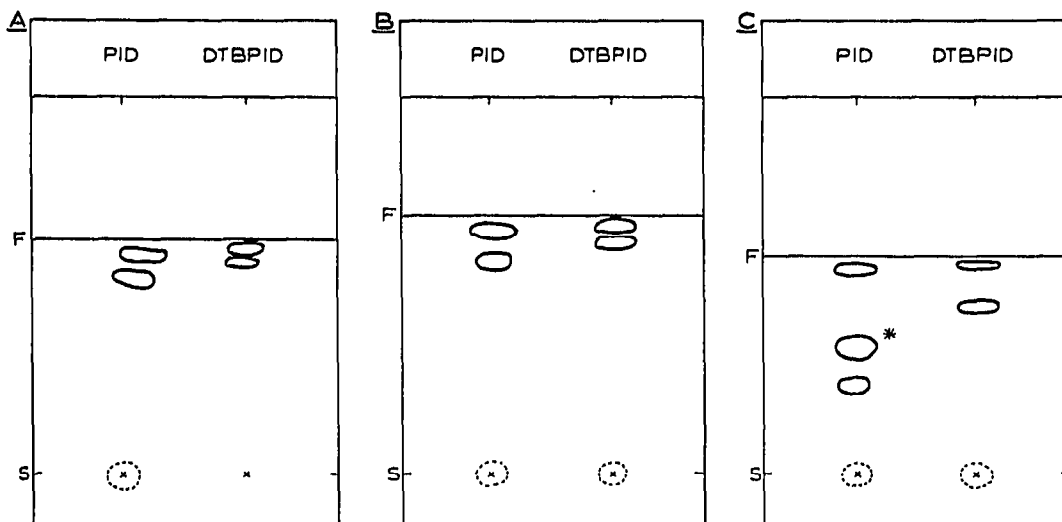


Fig. 5. A, Chromatographic analysis of 2-phenyl-1,3-indandione and 2-(3,5-di-*tert.*-butylphenyl)-1,3-indandione using a (C) plate and solvent (b). Indandiones were applied on exposure to air, and eluted 30 min later. B, As in A, but by means of a halved (A) plate. C, As in A, but by means of a halved (B) plate. * $R_F = 0.58$. Daenens and Van Boven¹⁴ used silica gel G "nach Stahl" as the carrier and chloroform-methanol (97:3) as the eluent, and obtained an R_F value of 0.54. For the abbreviations PID and DTBPID, see Figs. 1 and 2. F = front; S = start.

the extracts of a silica gel layer on which IV had been chromatographed were determined; the results are given in Fig. 6.

The fact that in spot *a* mainly m/e 350 was demonstrated pointed to the incorporation of oxygen. In spot *b*, unconverted indandione was the major component, and probably spot *c* contained the "dimer". The finding of all three m/e values in spots *a* and *b* strongly suggests that oxidation had continued during the chromatographic process.

In order to check the results of the mass spectrometric examination, a number of potential conversion products, 3-phenyl-4-hydroxyisocoumarin (V, lactone), *o*-(phenylglyoxyloyl)benzoic acid (VI, benzil), 2,2'-diphenyl-[2,2'-biindan]-1,1',3,3'-tetrone (VII), 3-(3,5-di-*tert.*-butylphenyl)-4-hydroxyisocoumarin (VIII, lactone) and 2,2'-bis(3,5-di-*tert.*-butylphenyl)-[2,2'-biindan]-1,1',3,3'-tetrone (IX), were prepared (see Experimental) and their R_F values compared with those of the compounds formed on the thin layer. As V, VI and VII are known compounds, their analytical data are mentioned only under Experimental.

Compound VIII was first subjected to mass spectrometric analysis. It is evident from its spectrum (Fig. 7) that the m/e value of 350 refers to the molecular ion. In addition, the fragment ions may together be considered as having resulted from the lactone structure indicated by the spectrum.

On comparison of the NMR spectra of IV and VIII, the following can be noted. The aromatic pattern in the spectrum of what is presumably the lactone (Fig. 8) has fairly much in common with that of the starting material (Fig. 9), suggesting that the aromatic rings are still intact.

| | Spot | m/e |
|---|------|---|
| c | c | <u>666</u> |
| b | b | mainly <u>334</u> 350 as well 666 as well |
| a | a | mainly <u>350</u> 334 as well 666 as well |

Fig. 6. Results of a mass spectrometric study on the residues of extracts of a silica gel layer on which 2-(3,5-di-*tert.*-butylphenyl)-1,3-indandione had been chromatographed. F == front; S == start.

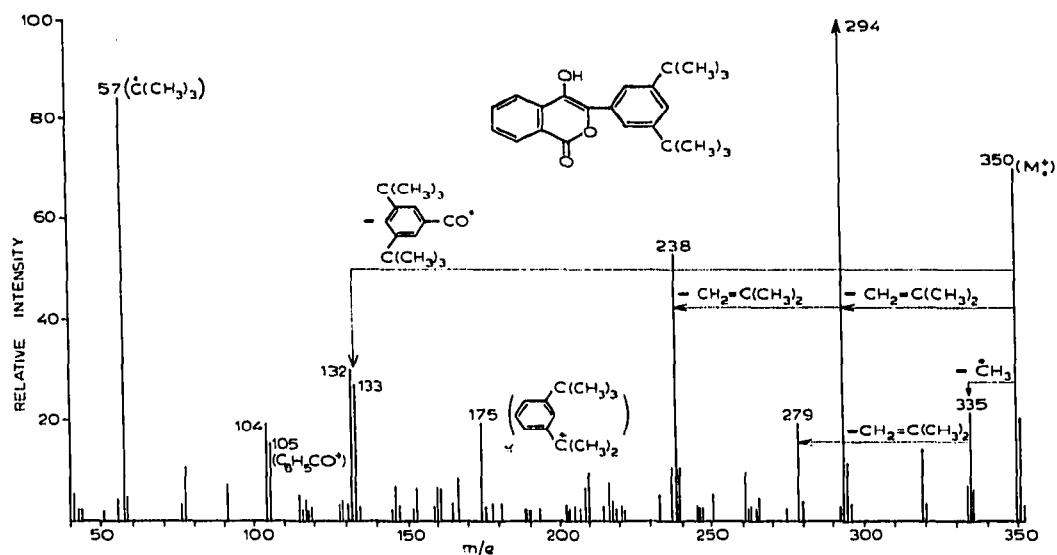


Fig. 7. Mass spectrum of 3-(3,5-di-*tert.*-butylphenyl)-4-hydroxyisocoumarin.

The signal of the two *ortho*-hydrogen atoms on the substituted phenyl nucleus has shifted downfield. This may be in agreement with the introduction of an oxygen atom into the chemical environment of these two hydrogen atoms. Another feature revealed by the comparison is the replacement of the hydrogen atom on the five-membered ring with an exchangeable proton, thus suggesting the presence of a hydroxyl group. An IR spectrum of VIII was also run. A band at 3460 cm^{-1} supported the presence of a hydroxyl group. In the analysis of IX, mass spectrometry and NMR spectroscopy were applied. The mass spectral data, as shown in Fig. 10, make it very likely that the m/e value of 666 refers to the molecular ion. The pattern of the remaining m/e s points clearly to the biindantetrone structure.

In the NMR spectrum (Fig. 11), the aromatic pattern appears to indicate that the aromatic system of the indandione had remained unchanged. Again, the hydrogen atom on the five-membered ring has disappeared.

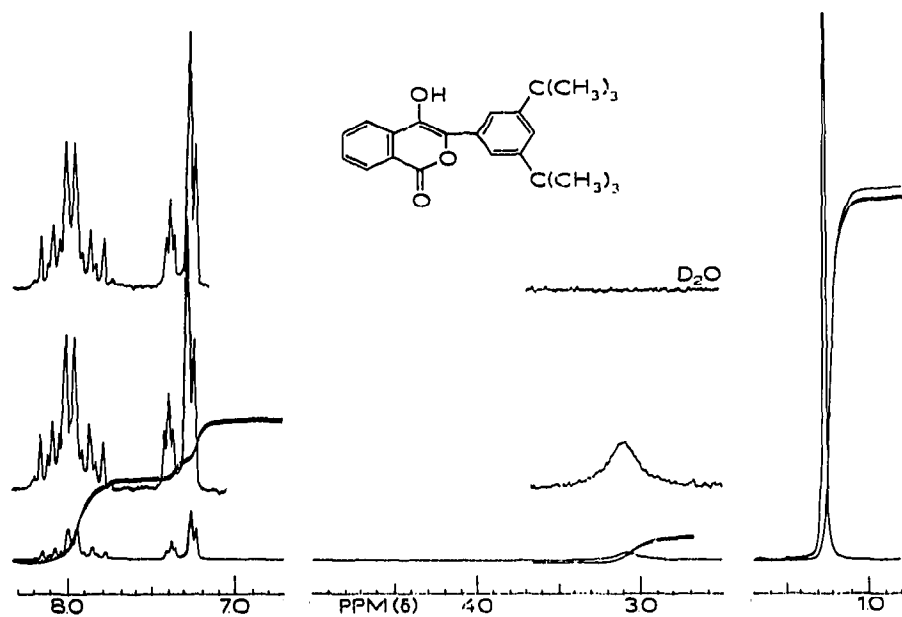


Fig. 8. NMR spectrum of 3-(3,5-di-*tert.*-butylphenyl)-4-hydroxyisocoumarin.

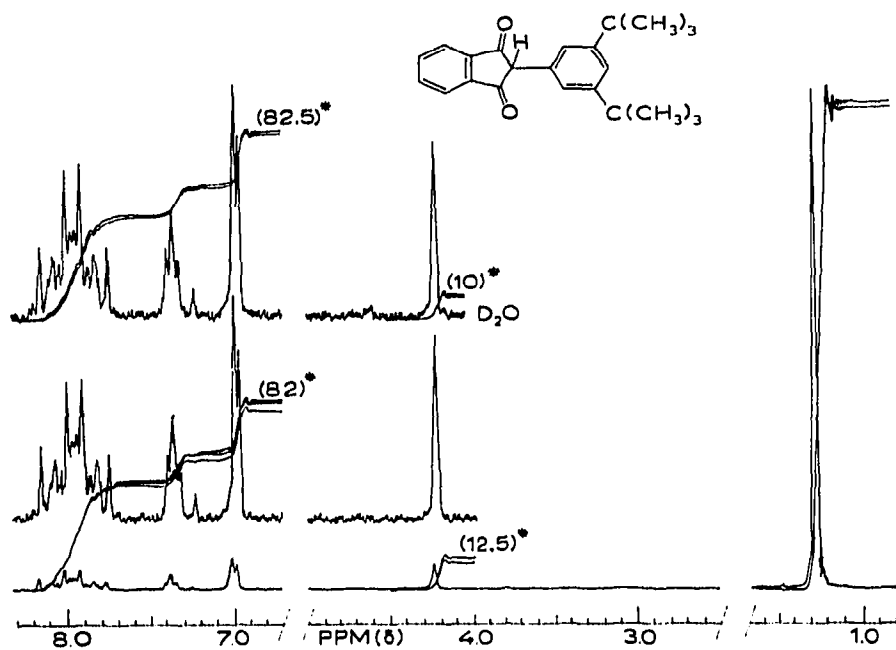


Fig. 9. NMR spectrum of 2-(3,5-di-*tert.*-butylphenyl)-1,3-indandione. *Integrated absorption.

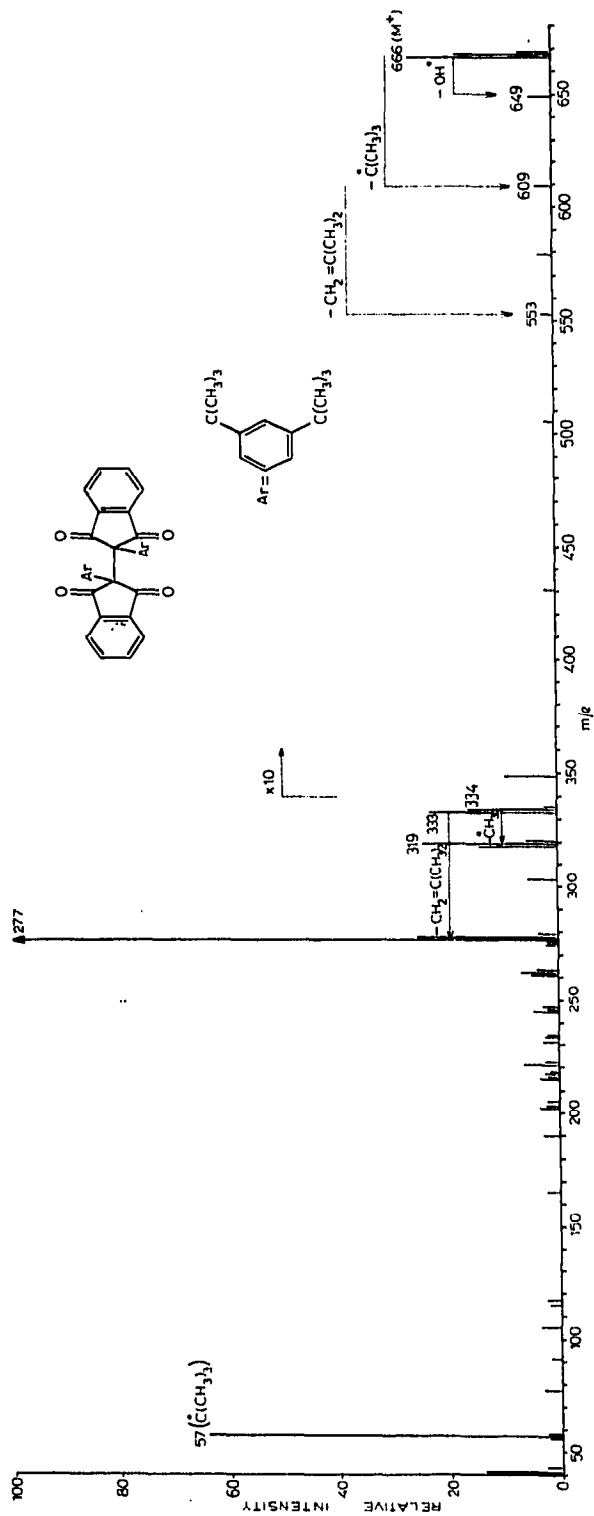


Fig. 10. Mass spectrum of 2,2'-bis(3,5-di-*tert*-butylphenyl)-[2,2'-biindan]-1,1',3,3'-tetrone.

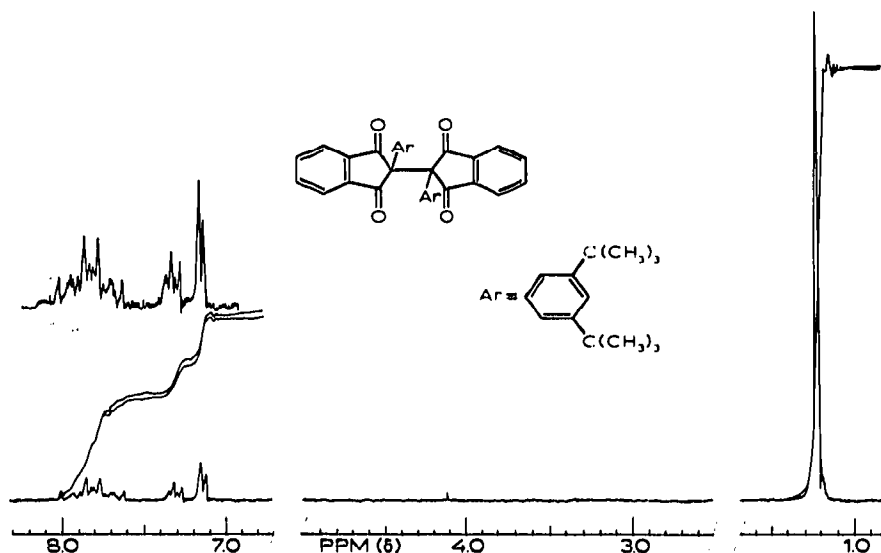


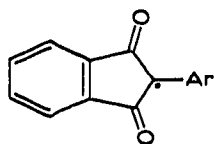
Fig. 11. NMR spectrum of 2,2'-bis(3,5-di-*tert.*-butylphenyl)-[2,2'-biindan]-1,1',3,3'-tetrone.

Comparison of the R_F values in Figs. 1 and 2 finally confirmed that the spots *a*, *b* and *c* were produced by the hydroxyisocoumarins, indandiones and biindantetrone, respectively. In the case of phenylindandione, the fourth, very weak, spot at the starting point was identified as VI.

Stability

Stability on the thin layer. Inspection of the thin-layer chromatograms obtained by elution 30 min after application of the indandiones from freshly prepared ethanolic solutions shows immediately that II and III were more stable than I and IV on the silica gel in air (see Figs. 1–3). On the other hand, II and III did undergo conversions on silica gel, as appears from the chromatograms in Fig. 3, which were obtained by elution after a 24-h exposure to air on the plates.

For conversions and reactions of 2-aryl-1,3-indandiones in solution, various workers^{3,15–17} have proposed mechanisms that have the following radical in common:



Ar=aryl

Such a radical will be stabilized by resonance. Assuming that the conversion of arylindandiones when exposed to air on silica gel may occur via similar radical mechanisms, the following might serve as an explanation of the greater stability of 2-(2,6-dialkylphenyl)-1,3-indandiones. In the case of the radical of a 2,6-dialkylphenyl-

indandione, there will be fewer possibilities of mesomerism and hence less chance of its formation. In discussing the NMR spectra of 2,6-dialkylphenylindandiones, Beringer and Galton¹⁶ and Bruynes⁷ pointed out that these strongly suggest that the 2,6-dialkylphenyl group lies in a plane perpendicular to the plane of the indandione group. If there is a similar perpendicular position in the radical, as is suggested by the steric effects of the two *ortho* groups, then the parallel position of the *p*-orbital of C₁ of the 2,6-dialkylphenyl group and the *p*-orbital of C₂ of the indandione group, and thus resonance, should be impaired.

Stability in solution. Only in the case of IV were air-exposed solutions tested for conversions. To this end, IV was dissolved in ethanol and in benzene. There appears to be a linear relationship between $\log [I]/[I_0]$ (where $[I_0]$ = initial concentration of the indandione) and time in both media (*cf.*, Fig. 12). It might be concluded that in both solutions the indandione is converted in a first-order reaction.

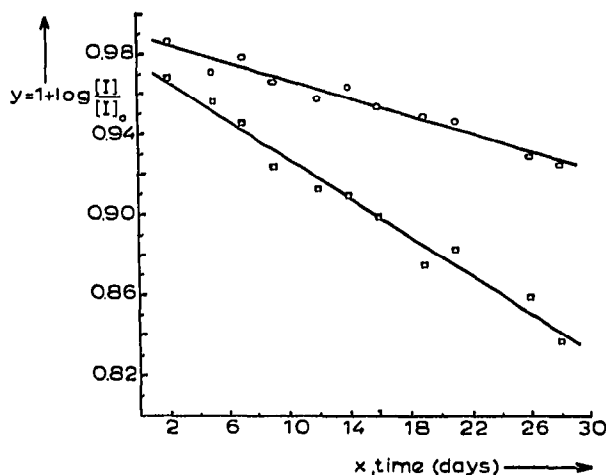


Fig. 12. Oxidation of 2-(3,5-di-*tert.*-butylphenyl)-1,3-indandione in the air. In absolute ethanol (O): $y = 0.9889 - 0.0022x$ with $s_{y \cdot x} = 0.0032$, $r = 0.978$, $s_{\ln r} = 0.00015$ and $T = -14.081$. In benzene (□): $y = 0.9756 - 0.0048x$ with $s_{y \cdot x} = 0.0063$, $r = 0.988$, $s_{\ln r} = 0.00024$ and $T = -19.533$.

While on silica gel the conversion into the lactone was fastest (see scan in Fig. 4), in solution the "dimer" was the main product (see Fig. 13).

Fig. 13 also shows, however, that lactone was produced to some extent. "Dimerization" was faster in apolar benzene than in polar ethanol. It would appear that again a radical mechanism is involved, as already suggested by Rigaudy and Aubrun³ for the "dimerization" of unsubstituted phenylindandione.

CONCLUSIONS

In order to avoid oxidation, it is necessary to perform all those activities with arylindandiones that require some time, such as synthesis, purification, analysis (for example, by means of UV spectrophotometry) and preparation of dosage forms, in a nitrogen atmosphere. It is necessary to establish whether any contact of an aryl-

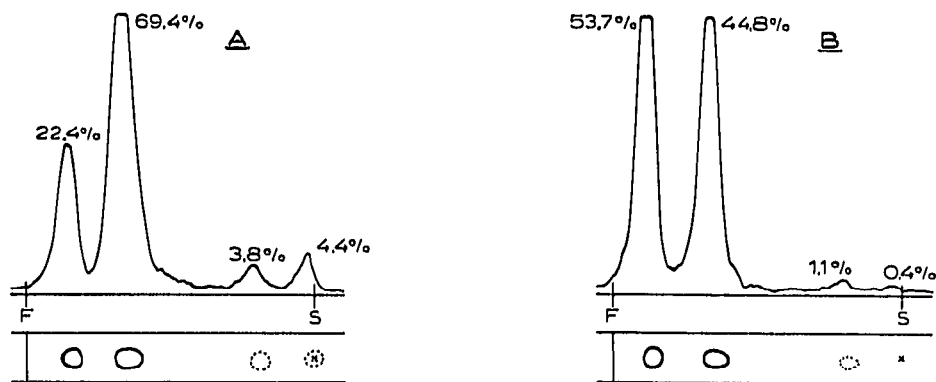


Fig. 13. A, Chromatogram and scan of 2-(3,5-di-*tert.*-butylphenyl)-1,3-[di- ^{14}C]indandione on an (A) plate following elution with solvent (a). An ethanolic solution of the indandione was exposed to air for 2 months. Application in a nitrogen atmosphere. B, As in A, but using a benzene solution of the indandione.

indandione with other materials may influence the rate and route of oxidation on exposure to air. The stability of a phenylindandione on exposure to air may be changed by alterations in the substitution pattern of the phenyl nucleus.

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