

1-BROMO-1,2,2-TRIARYLETHYLENES OF THE XANTHENE SERIES

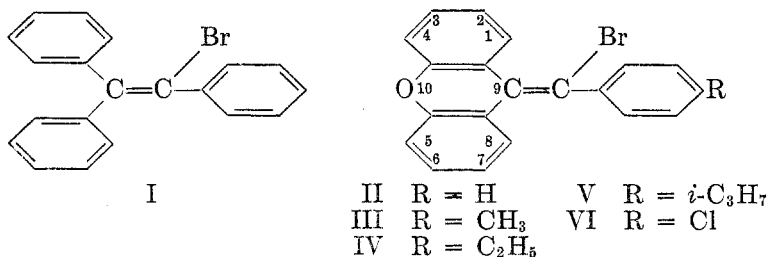
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As a result of an increasing number of observations arising from the broad clinical utilization of natural and synthetic estrogens, the over-all biological activity of these molecules can no longer be estimated solely in relation to their potency in the Allen-Doisy test. Thus, stilbestrol is therapeutically more valuable than hexestrol (1), which shows greater potency in the Allen-Doisy test; similarly, stilbestrol-resistant cancers of the prostate reportedly have been successfully treated with weaker estrogens such as dienestrol (2) and 1-bromo-1,2,2-triphenylethylene (3), although the Allen-Doisy activity of the latter has been found to be several hundred times less than that of stilbestrol (4). There is thus some hope for avoiding, in prostate-cancer chemotherapy, serious inconveniences such as impotence and the occurrence of tumors of the breast, which are inherent in the use of powerful estrogens.

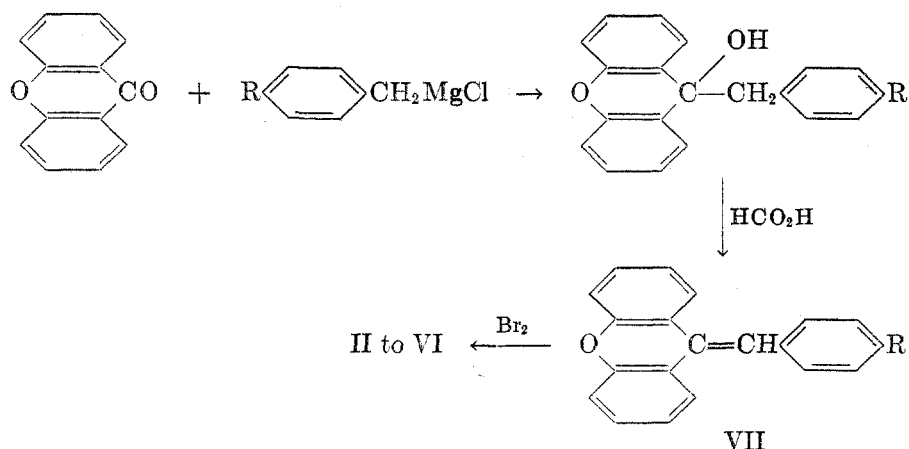
These considerations led us to investigate compounds bearing a close molecular resemblance with 1-bromo-1,2,2-triphenylethylene (I) but even less estrogenic than the latter. In the present work, the introduction of xanthene nuclei is considered, in view of the known weakening effect of *ortho*-substituents in the 1,2,2-triarylethylene series (5).

9-(ω -Bromobenzal)xanthene (II), the most simple compound of the present series, had already been prepared by Bergmann and von Christiani (6), through heating the "tetrabromide" obtained in the bromination of 9-benzalxanthene

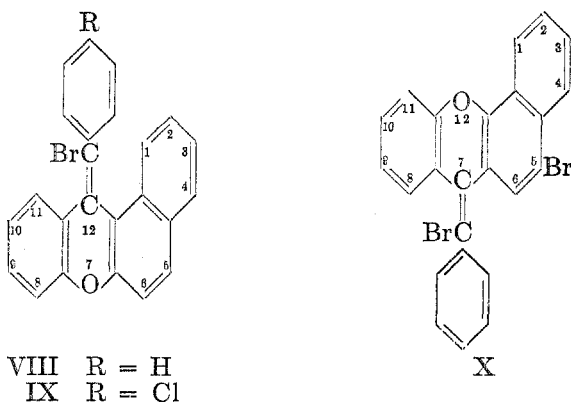


in chloroform medium. We have now found that compound II could be obtained more conveniently in almost quantitative yield by bromination of 9-benzalxanthene in acetic acid; in this case, only one molecule of halogen was required, and the formation of a "perbromide" was avoided. The same method was successfully used in the preparation of 9-(ω -bromo-*p*-methylbenzal)xanthene (III), 9-(ω -bromo-*p*-ethylbenzal)xanthene (IV), 9-(ω -bromo-*p*-isopropylbenzal)xanthene (V), and 9-(ω -bromo-*p*-chlorobenzal)xanthene (VI). Among the intermediates (VII) used, 9-*p*-chlorobenzalxanthene had already been described by Conant and Small (7); and 9-*p*-methyl-, 9-*p*-ethyl-, and 9-*p*-isopropyl-benzalxanthene were prepared by formic acid-dehydration of the tertiary xanthydrals obtained

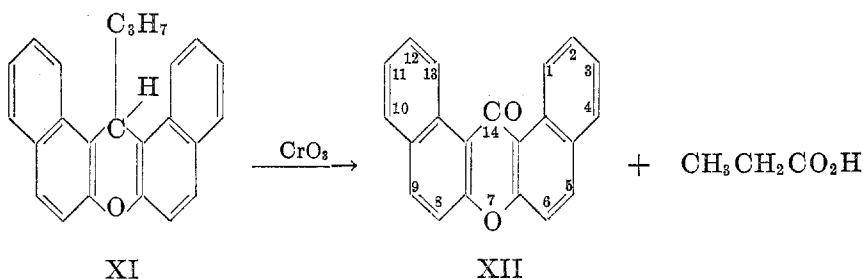
in the interaction of xanthone and the Grignard reagents from *p*-methyl-, *p*-ethyl-, and *p*-isopropyl-benzyl chloride:



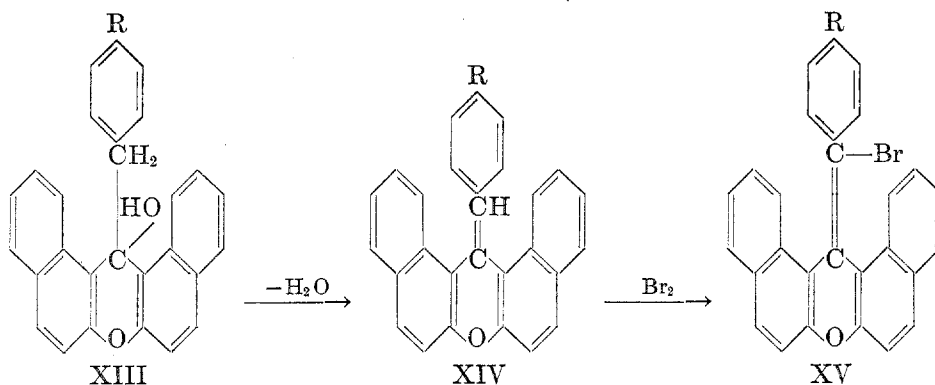
An extension of this work to the 12-benzo[*a*]xanthene and 7-benzo[*c*]xanthene systems led to an interesting observation. Although 12-benzal-12-benzo[*a*]xanthene could be readily converted in the usual way to 12-(ω -bromobenzal)-12-benzo[*a*]xanthene (VIII), and 12-(*p*-chlorobenzal)-12-benzo[*a*]xanthene to 12-(ω -bromo-*p*-chlorobenzal)-12-benzo[*a*]xanthene (IX), a *dibromo compound* was obtained when the same technique was applied to 7-benzal-7-benzo[*c*]xanthene. This anomaly is apparently due to the fact that in the molecule of 7-benzal-7-benzo[*c*]xanthene, position 5, *para* to the oxygen heteroatom, is available for substitution; the dibromo compound cited is thus probably 5-bromo-7-(ω -bromobenzal)-7-benzo[*c*]xanthene (X).



During the present research, it was found that the directions given in the literature for the synthesis of 12-benzo[*a*]- and 7-benzo[*c*]-xanthone (8) were inadequate, and a modified procedure had to be worked out for the preparation of these compounds. Similarly, the synthesis of 14-dibenzo[*a, j*]xanthone (XII)



was improved by replacing the chromic oxidation of 14-methyl-14-dibenzo[*a, j*]-xanthene (9) by that of a higher homolog such as 14-*n*-propyl-14-dibenzo[*a, j*]-xanthene (XI). The easier oxidation of the latter is most likely due to the presence of a methylene group attached to the xanthene nucleus instead of a less reactive methyl group; in fact, a good yield of propionic acid was simultaneously obtained. 14-Dibenzo[*a, j*]xanthone reacted with benzylmagnesium chloride and with *p*-methyl-, *p*-ethyl-, and *p*-chloro-benzylmagnesium chloride to give well-crystallized, colorless 14-benzyl-14-dibenzo[*a, j*]xanthydrols (XIII), which readily lost



water upon solution in hot acetic acid to give the corresponding yellow 14-benzal-14-dibenzo[*a, j*]xanthenes (XIV). On bromination, the latter gave the corresponding 14-(ω -bromobenzal)-14-dibenzo[*a, j*]xanthenes (XV), which are listed in the Table together with the intermediates involved in their preparation.

EXPERIMENTAL

Preparation of 9-(ω -bromobenzal)zanthene. 9-Benzalxanthene was prepared by refluxing for some minutes a solution of 9-benzalxanthanol in 98% formic acid, the reaction mixture being then poured into water and the ethylene compound taken up in benzene; it formed from ethanol long, colorless needles, m.p. 116°, giving with sulfuric acid a canary-yellow color. An ice-cooled, well-stirred solution of 5.4 g. of 9-benzalxanthene in acetic acid was treated dropwise with bromine (3.2 g. dissolved in 10 ml. of acetic acid). Disappearance of the bromine and evolution of hydrogen bromide took place immediately, and after ten minutes at room temperature the mixture was diluted with water. The solid obtained gave, on recrystallization from ethanol, long shiny colorless needles, m.p. 113° (literature m.p. 110°), giving with sulfuric acid a yellow coloration. The yield was almost quantitative.

9-(*p*-Methylbenzal)xanthene (VII; R = CH₃). A Grignard reagent made from 1.8 g. of

magnesium shavings and 11 g. of *p*-methylbenzyl chloride in ether was treated with 10 g. of xanthone (dissolved in several ml. of benzene); the reaction mixture was subsequently refluxed for 15 minutes, and was decomposed after cooling with an iced aqueous solution of ammonium chloride. The crude xanthidrol thus obtained was directly dehydrated with 98% formic acid, and the xanthene formed was purified by vacuum-distillation. It crystallized from acetic acid or ethanol in lustrous, greenish-tinged leaflets, m.p. 114°, b.p. 265–269°/14 mm., giving with sulfuric acid a yellow coloration. Yield: 12 g.

Anal. Calc'd for $C_{21}H_{16}O$: C, 88.7; H, 5.6.

Found: C, 88.5; H, 5.7.

9-(ω-Bromo-p-methylbenzal)xanthene (III). Halogenation of the foregoing compound (2.84 g.) with 1.6 g. of bromine was effected as above in acetic acid. A 95% yield was obtained of a compound forming from acetic acid lustrous, colorless leaflets, m.p. 146°.

Anal. Calc'd for $C_{21}H_{15}BrO$: C, 69.4; H, 4.1.

Found: C, 69.2; H, 4.1.

9-(p-Ethylbenzal)xanthene (VII; $R = C_2H_5$). Obtained from 10 g. of xanthone and a Grignard reagent made from 13 g. of *p*-ethylbenzyl chloride (the latter was prepared by chloromethylation of ethylbenzene), and subsequent formic dehydration of the xanthidrol formed. After purification by vacuum-distillation (b.p. 272–274°/13 mm.), it crystallized from acetic acid in fine, faintly greenish-yellow needles, m.p. 96°.

Anal. Calc'd for $C_{22}H_{18}O$: C, 88.6; H, 6.04.

Found: C, 88.5; H, 6.3.

9-(ω-Bromo-p-ethylbenzal)xanthene (IV). Prepared from 1 g. of the preceding compound and 0.54 g. of bromine, it formed from acetic acid shiny colorless needles, m.p. 112°.

Anal. Calc'd for $C_{22}H_{17}BrO$: C, 70.0; H, 4.5.

Found: C, 69.7; H, 4.8.

9-(ω-Bromo-p-isopropylbenzal)xanthene (V). *9-(p-Isopropylbenzal)xanthene*, prepared in the usual way from xanthone and *p*-isopropylbenzyl chloride (obtained by chloromethylation of cumene), was purified by vacuum-distillation (b.p. 278–280°/13 mm.), but could not be brought to crystallization. When 5.5 g. of this viscous yellow resin was treated with 2.82 g. of bromine, however, it gave a crystalline product, which formed from acetic acid colorless, lustrous leaflets, m.p. 119°.

Anal. Calc'd for $C_{23}H_{19}BrO$: C, 70.6; H, 4.85.

Found: C, 70.3; H, 5.0.

9-(ω-Bromo-p-chlorobenlal)xanthene (VI). *9-(p-Chlorobenlal)xanthene* was prepared according to Conant and Small (7), and purified by vacuum-distillation (b.p. 280°/15 mm.); it formed from acetic acid greenish-tinged needles, m.p. 137°. This ethylene (5 g.), treated with 2.7 g. of bromine, gave in quantitative yield a substitution product, crystallizing from acetic acid in fine shiny colorless needles, m.p. 158°.

Anal. Calc'd for $C_{20}H_{12}BrClO$: C, 62.6; H, 3.12.

Found: C, 62.4; H, 3.5.

Preparation of 12-benzo[a]- and 7-benzo[c]xanthone. A mixture of 28 g. of dried salicylic acid, 29 g. of β -naphthol, and 60 g. of acetic anhydride was refluxed for ten hours; the acetic acid formed was then removed, along with the excess of acetic anhydride, by very slow distillation. Heating at normal pressure was continued until the temperature reached 290–300°, and the residue was vacuum-fractionated. The portion boiling at 310–320°/40 mm. was collected and recrystallized from a mixture of ethanol and benzene (the forerun consisted mainly of xanthone). The yield was at least 15 g. of 12-benzo[a]xanthone, in the form of long silky pale yellow needles, m.p. 143°.

A similar reaction, performed with α -naphthol, yielded 7-benzo[c]xanthone, boiling at about 310–320°/40 mm., and forming from benzene and ethanol pale yellow leaflets, m.p. 156°.

12-(ω-Bromobenlal)-12-benzo[a]xanthene (VIII). 12-Benzal-12-benzo[a]xanthene (10) was prepared from 4.5 g. of 12-benzo[a]xanthone and a Grignard reagent made with 1.1 g. of magnesium and 8 g. of benzyl chloride, with subsequent formic acid dehydration of the

12-benzyl-12-benzo[*a*]xanthidrol; bromination, effected as for the 9-benzalxanthenes, gave compound VIII, which formed from acetic acid fine colorless prisms, m.p. 152° (98% yield).

Anal. Calc'd for $C_{24}H_{18}BrO$: C, 72.1; H, 3.7.

Found: C, 72.3; H, 3.6.

12-(ω -Bromo-*p*-chlorobenzal)-12-benzo[*a*]xanthene (IX). Prepared from 1.8 g. of the corresponding ethylene (not isolated) and 0.8 g. of bromine, it formed from acetic acid fine colorless prisms, m.p. 171°.

TABLE I
14-SUBSTITUTED 14-DIBENZO[*a, j*]XANTHENES: XIII, XIV, AND XV

COMPOUND	R	FORMULA	M.P., °C.	ANALYSES			
				Calc'd		Found	
				C	H	C	H
14-Benzyl-14-hydroxy	XIII; R = H	$C_{28}H_{26}O_2$	188	86.5	5.1	86.7	5.4
14-Benzal ^a	XIV; R = H	$C_{28}H_{18}O$	166	90.8	4.8	90.5	4.8
14- ω -Bromobenzal	XV; R = H	$C_{28}H_{17}BrO$	202	74.8	3.7	74.6	3.6
14- <i>p</i> -Methylbenzyl-14-hydroxy	XIII; R = CH_3	$C_{29}H_{22}O_2$	189	86.5	5.4	86.4	5.6
14- <i>p</i> -Methylbenzal	XIV; R = CH_3	$C_{29}H_{20}O$	176	90.6	5.2	90.3	5.2
14-(ω -Bromo- <i>p</i> -methylbenzal)	XV; R = CH_3	$C_{29}H_{19}BrO$	191	75.1	4.1	74.9	4.0
14- <i>p</i> -Ethylbenzyl-14-hydroxy	XIII; R = C_2H_5	$C_{30}H_{24}O_2$	157	86.5	5.7	86.4	5.9
14- <i>p</i> -Ethylbenzal	XIV; R = C_2H_5	$C_{30}H_{22}O$	129	90.4	5.5	90.1	5.4
14-(ω -Bromo- <i>p</i> -ethylbenzal)	XV; R = C_2H_5	$C_{30}H_{21}BrO$	177	75.4	4.7	75.3	4.4
14- <i>p</i> -Chlorobenzyl-14-hydroxy	XIII; R = Cl	$C_{28}H_{16}ClO_2$	242	79.5	4.5	79.2	4.7
14- <i>p</i> -Chlorobenzal	XIV; R = Cl	$C_{28}H_{17}ClO$	171	83.0	4.2	82.6	4.5
14-(ω -Bromo- <i>p</i> -chlorobenzal)	XV; R = Cl	$C_{28}H_{16}BrClO$	216	69.4	3.3	69.1	3.2

^a All compounds of Formula XIV gave with sulfuric acid a deep orange coloration; a lighter coloration was produced by compounds of Formula XV.

Anal. Calc'd for $C_{24}H_{14}BrClO$: C, 66.4; H, 3.2.

Found: C, 66.1; H, 3.0.

5-Bromo-7-(ω -bromobenzal)-7-benzo[*c*]xanthene (X). The corresponding ethylene was prepared from 4 g. of 7-benzo[*c*]xanthone, 8 g. of benzyl chloride, and 1.1 g. of magnesium (yield, 4 g.). It was directly treated with 2 g. of bromine in the usual way, and gave a *disubstitution product*, forming from acetic acid fine colorless prisms, m.p. 184°.

Anal. Calc'd for $C_{24}H_{14}Br_2O$: C, 60.2; H, 2.9.

Calc'd for $C_{24}H_{15}BrO$: C, 72.1; H, 3.7.

Found: C, 60.2; H, 3.0.

14-*n*-Propyl-14-dibenzo[*a, j*]xanthene (XI). To a boiling solution of 15 g. of β -naphthol and 8 g. of *n*-butyraldehyde in 50 ml. of ethanol, 3 ml. of hydrochloric acid was added dropwise; the mixture was then refluxed for five minutes, and kept overnight at room temperature. The solid precipitate was collected, washed with methanol, and recrystallized from ethanol. Yield, 18 g. of long colorless prisms, m.p. 161°, giving no coloration with sulfuric acid.

Anal. Calc'd for $C_{24}H_{20}O$: C, 88.9; H, 6.2.

Found: C, 88.8; H, 6.2.

Preparation of 14-dibenzo[a, j]xanthone. To a boiling solution of 12 g. of the preceding xanthene in 100 ml. of acetic acid, a suspension of 20 g. of chromic acid in 60 ml. of acetic acid was added in small portions. When the violent reaction had subsided, the mixture was refluxed for some minutes, and kept overnight after dilution with 20 ml. of water. The solid precipitate (9.5 g.) crystallized from acetic acid in shiny pale yellow prisms, m.p. 197° [literature m.p. 194° (8)]. Some of the same ketone was obtained by further dilution of the filtrate with water.

SUMMARY

1. For cancer research, a large number of analogs of 1-bromo-1,2,2-triphenyl-ethylene have been prepared in the xanthene, 12-benzo[a]-, 7-benzo[c]-, and 14-dibenzo[a, j]-xanthene series.

2. The preparation of 12-benzo[a]-, 7-benzo[c]-, and 14-dibenzo[a, j]-xanthene has been improved.

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REFERENCES

- (1) BISHOP, *Lancet*, II, 764 (1948).
- (2) COX, *Brit. Med. J.*, II, 191 (1946).
- (3) BERGER AND BUU-HOÏ, *Lancet*, II, 173 (1947).
- (4) LACASSAGNE, BUU-HOÏ, CORRE, LECOCQ, AND ROYER, *Experientia*, **2**, 70 (1946).
- (5) See BUU-HOÏ AND LECOCQ, *J. Chem. Soc.*, 641 (1947).
- (6) BERGMANN AND VON CHRISTIANI, *Ber.*, **63**, 2559 (1930).
- (7) CONANT AND SMALL, *J. Am. Chem. Soc.*, **47**, 3068 (1925).
- (8) VON KOSTANECKI, *Ber.*, **25**, 1643 (1892).
- (9) CLAUS AND RUPPEL, *J. prakt. Chem.*, [2] **41**, 49 (1890).
- (10) MUSTAFA, *J. Chem. Soc.*, S. 83 (1949).