[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF NOTRE DAME]

PHOTOBROMINATION OF SUBSTITUTED TOLUENES AS A ROUTE TO SUBSTITUTED BENZYL ALCOHOLS AND BENZALDEHYDES

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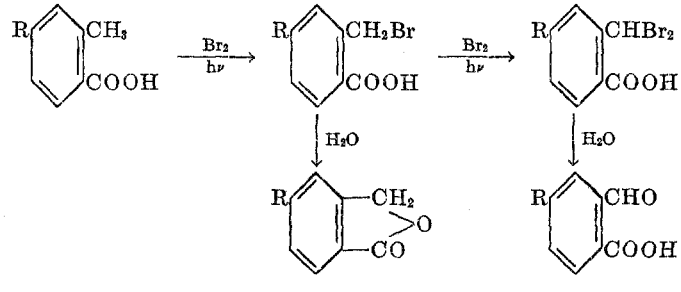
In connection with another problem we became interested in the synthesis of ring-substituted phthalides (I) and phthalaldehydic acids (II). While a number of methods are available for the synthesis of the unsubstituted compounds (1–13), most of these utilize phthalic anhydride (1–6, 13) or naphthalene (7) as a starting material. Such methods, when applied to the synthesis of substituted phthalides and phthalaldehydic acids would be expected to yield mixtures (Ia,b; IIa,b), or, at best, compounds of doubtful structure. It appeared that the synthesis of compounds of unequivocal identity could be accomplished by photobromination of suitably substituted toluic acids, followed by hydrolysis of the resulting benzyl or benzal bromides:



The idea of synthesizing phthalide and phthalaldehydic acid in this or similar ways is not new (8–11), but in the earlier procedures yields were either not given (8–10) or were stated to be poor (11). Moreover, the bromination was usually carried out at temperatures at which the bromine is in the gas phase which is far from convenient. In fact, a survey of the literature on photobromination of side chains in general indicates that while the reaction has attracted

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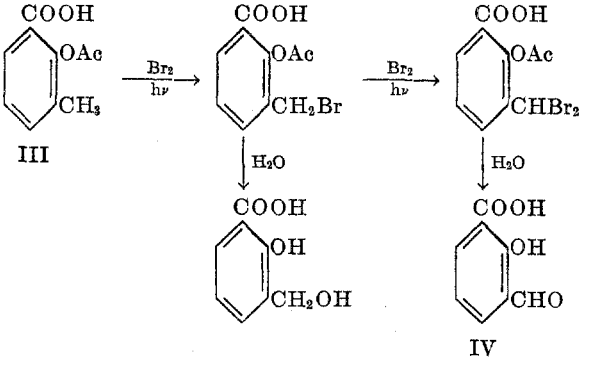
considerable interest from the theoretical point of view (14), its practical applications have been rather limited (11, 15–22). The conditions under which bromination has been effected are far from standard. In some cases sunlight was employed as a source of energy (11, 15, 18) in others a mercury arc lamp (18, 21), in still others a tungsten lamp (16, 17, 19, 20). One procedure specifies strictly anhydrous conditions (16), in another (21) water was deliberately added to dissolve the hydrogen bromide formed in the reaction. On occasions, a small amount of iodine has been added as a "catalyst" in photobromination (15, 21).

The only agreement among the various procedures seems to be with respect to the solvent which is almost always either carbon tetrachloride or carbon disulfide, though in a few cases (17, 19) a solvent is not employed.

Our experiments with *o*-toluic acid indicate that this compound can be either photomonobrominated or photodibrominated in good yield in carbon tetrachloride solution at the reflux temperature in the presence of a tungsten lamp. The presence of a water layer during the reaction seems to be without appreciable influence on the yield or the rate of the reaction (*cf.* 18) and would appear to be definitely undesirable when the compounds under study have hydrolyzable functional groups (16). Iodine, far from being a catalyst, is a marked inhibitor of the photobromination reaction and in some cases causes the reaction to fail entirely. Thus methyl *o*-toluate can be readily photobrominated in the absence of iodine, but not in its presence. It had previously been noted (18) that sulfur is a negative catalyst for photobromination.

Since some of the substituted phthalaldehydic acids we were interested in contain phenolic groups, we have studied the photobromination of the commercially available *o*-cresotinic acid in the form of its acetyl derivative (III) by way of a model reaction. Again both photomonobromination and photodibromination proceeded readily and the resulting halides could be hydrolyzed to the corresponding benzyl alcohol and benzaldehyde, compounds which are not readily available by other routes. The synthesis of 3-formylsalicylic acid (IV) resembles that of 4-nitrosalicylaldehyde from 4-nitro-*o*-cresyl acetate reported in the literature (16).



Further examples of this reaction will be reported later in another connection.

EXPERIMENTAL

The photobrominations reported in this paper were studied under a variety of conditions, such as presence and absence of iodine, presence and absence of water, and varying rates of addition of bromine. The following general procedure was found to be most satisfactory.

TABLE I

PHOTOBROMINATION OF SUBSTITUTED TOLUENES

COMPOUND BROMINATED	MOLE RATIO Br_2/Compound	PRODUCT	M.P., °C.[a]	YIELD,[a] %
Acetyl-*o*-cresotinic acid	1:1	Acetyl-ω-bromo-*o*-cresotinic acid	131–132 (dec.)[b]	70
	2:1	Acetyl-ω,ω-dibromo-*o*-cresotinic acid	129–131[c]	68–75
o-Toluic acid	1:1	α-Bromo-*o*-toluic and	137–138 (dec.)[d]	84–94[e]
	2:1	α,α-Dibromo-*o*-toluic acid	160–161[f]	77
Methyl *o*-toluate	1:1	Methyl α-bromo-*o*-toluate	28.5–30[g]	66

[a] The melting points (uncorrected) and yields in the table refer to the crude product. [b] After recrystallization from ether-petroleum ether (b.p. 30–60°) the acid melted at 161–162° (dec.). *Anal.* Calc'd for $C_{10}H_9BrO_4$: C, 43.98; H, 3.32. Found: C, 44.00; H, 3.55. [c] Recrystallization from ether-petroleum ether gave m.p. 145–145.5°. *Anal.* Calc'd for $C_{10}H_8Br_2O_4$: C, 34.12; H, 2.29. Found: C, 35.89; H, 2.74; presumably indicating contamination with the monobromo acid. [d] Recrystallization gave m.p. 146.5–147° (dec.) (melting-point capillary inserted in block at 141°). Lit. (23) 147°. [e] This figure represents a conversion. A small amount of *o*-toluic acid was recovered. The yield of pure material was 79%. [f] After repeated recrystallization from ether-petroleum ether this acid melted at 170–171.5° but still contained some of the monobrominated compound as evidenced by the analysis. Calc'd for $C_8H_6Br_2O_2$: C, 30.68; H, 2.06. Found: C, 33.15, 33.22; H, 2.17, 2.31. However, the *methyl ester* (m.p. 51.5–52.5°), prepared from the acid and diazomethane, gave a satisfactory analysis: Calc'd for $C_9H_8BrO_2$: C, 35.10; H, 2.62. Found: C, 35.14; H, 2.63. The same ester resulted from the photobromination of methyl α-bromo-*o*-toluate. [g] The pure compound crystallized from ether-petroleum ether melted at 32–32.5°. *Anal.* Calc'd for $C_9H_9BrO_2$: C, 47.18; H, 3.96. Found: C, 47.33; H, 4.13. The same ester was obtained by treatment of the corresponding acid with diazomethane. However, photobromination of methyl *o*-toluate *in the presence of iodine* gave a different, though apparently isomeric material melting at 41–42°. (*Anal.* Calc'd for $C_9H_9BrO_2$: C, 47.18; H, 3.96; Br, 34.89. Found: C, 47.06; H, 4.13; Br, 34.58). Hydrolysis of this bromo compound with 10% aqueous-alcoholic sodium hydroxide followed by acidification yielded an unidentified compound of m.p. 48–50°.

Bromination. General procedure: In a 500-cc. 2-necked flask, fitted with a reflux condenser and a dropping-funnel, were placed 0.05 mole of the compound and 80 cc. of carbon tetrachloride. A 500-watt tungsten lamp was placed in an upright position about 2 cm. from the flask. The solution was gently refluxed while 0.05 mole (or 0.1 mole) or bromine in 80 cc. of carbon tetrachloride was added at such a rate that a red color persisted at all times. The reaction was completed when all the bromine was added and the red bromine color disappeared. For methyl *o*-toluate about 2 minutes was required while the dibromination of acetyl-*o*-cresotinic acid required about 2 hours.

The solution was allowed to cool to about 45° and petroleum ether (b.p. 30–60°) was added until the solution became turbid. The product was crystallized by cooling in a Dry Ice-acetone bath and was collected by suction filtration.

Results of the photobromination reactions are summarized in Table I.

Hydrolysis. General procedure: The compound (2 g.) was boiled under reflux for 1½ hours with 15–20 cc. of a dilute solution of acid or base (as indicated in Table II). If the solution was basic, it was acidified at the end of the reflux period. Where phthalide was the expected product the solution was warmed to complete lactonization. It was then concentrated and chilled in an ice-bath, whereupon the reaction products crystallized.

Results of the hydrolyses are summarized in Table II.

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TABLE II

HYDROLYSIS OF BROMINATED TOLUENES

COMPOUND HYDROLYZED	CONDITIONS	PRODUCT	M.P., °C.	YIELD, %
Acetyl-ω-bromo-*o*-cresotinic acid	10% Na_2CO_3 solution	α-Hydroxy-*o*-cresotinic acid	139.5–140.5[a]	45[b]
Acetyl-ω,ω-dibromo-*o*-cresotinic acid	8% Na_2CO_3 solution	3-Formylsalicylic acid	178–179[c]	76
α-Bromo-*o*-toluic acid	6% NaOH solution; acidify and warm	Phthalide	70–71.5[d]	75–82
α,α-Dibromo-*o*-toluic acid	3% NaOH or 8% HCl	Phthalaldehydic acid	96.5–97[e]	60

[a] Lit. (24) 142°. [b] Crude yield; material melting at 134–136°. [c] Lit. (25) 179°. The white colored *oxime* melted at 193°; Lit. (26), yellow needles, m.p. 193°. [d] Lit. (27) 73°. [e] Lit. (28) 97°.

SUMMARY

o-Toluic acid has been photobrominated to give either α-bromo-*o*-toluic acid or α,α-dibromo-*o*-toluic acid. Methyl *o*-toluate has been similarly brominated to give the monobromo derivative. The monobromo acid has been hydrolyzed to phthalide and the dibromo compound to phthalaldehydic acid.

Acetyl-*o*-cresotinic acid has been successfully mono- and di-brominated in the side chain. The resulting bromides have been hydrolyzed to 3-hydroxymethylsalicylic acid and 3-formylsalicylic acid.

All these reactions proceed in good yield.

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