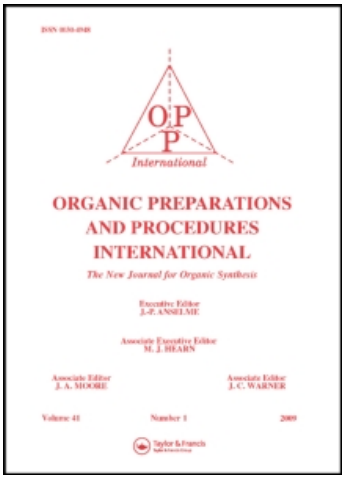

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A NEW ROUTE TO NITRO-AND BENZOYLPHTHALIDES

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OPPI BRIEFS

A NEW ROUTE TO NITRO- AND BENZOYLPHTHALIDES

Submitted by (10/26/88)

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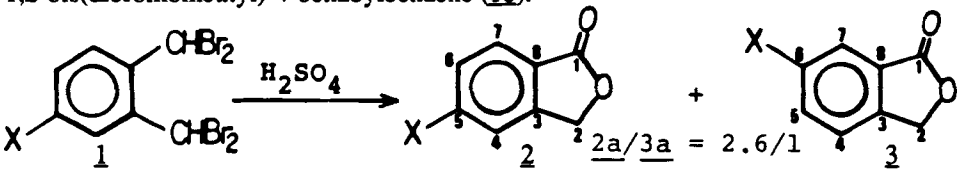
gem-Dihalides can be hydrolyzed under either acidic or basic conditions to give aldehydes or ketones,[1] as illustrated by the hydrolysis of 1,2-bis(dibromomethyl)benzene in fuming sulfuric acid to give o-phthalaldehyde.[2] We now report that 1,2-bis(dibromomethyl)- 4-nitrobenzene (1a) was hydrolyzed under acidic conditions to a mixture of 5- and 6- nitrophthalides, instead of the expected 4-nitro-o-phthalaldehyde; a similar result was observed for the hydrolysis of 1,2-bis(dibromomethyl)-4-benzoylbenzene (1b).



a) X = NO_2 b) X = COPh

2a/3a = 2.6/1

2b/3b = 2.0/1

The structures of these substituted phthalides (2a,b and 3a,b) were elucidated on the basis of spectral data (Tables), and in the case of 3a, an authentic sample, prepared according to the procedure of Houbion,[3] was identical in all respects with our product.

The present work provides an alternative method to the known procedures[4-9] for the preparation of these substituted phthalides. The effect of electron-donating substituents (-X) on this hydrolysis reaction and the mechanism of this reaction are under study.

TABLE 1. Yields, mps. and Spectral Data of 2 and 3

Compd.	mp. (°C)	Yield (%)	C = O (cm^{-1})	^1H nmr (δ ppm, $CDCl_3$)
2a	150 (151)[10]	61*	1750	5.45 (s, 2H, $-CH_2O-$), 8.10 (d, 1H, $-C^7H-$), 8.37-8.47 (m, 2H, ArH)
3a	141 (143)[10]		1740	5.45 (s, 2H, $-CH_2O-$), 7.72 (d, 1H, $-C^4H-$), 8.57 (d, 1H, $-C^5H-$), 8.75 (s, 1H, $-C^7H-$)
2b	147	54*	1745	5.40 (s, 2H, $-CH_2O-$), 7.44-8.08 (m, 8H, ArH)
3b	151		1740	5.42 (s, 2H, $-CH_2O-$), 7.50-8.25 (m, 8H, ArH)

*Total yield of the two isomers.

TABLE 2. ^{13}C nmr Spectral Data(ppm) of 2 and 3

Compd.	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8
2a	168.3	69.4	147.3	117.9	151.5	124.6	127.0	130.7
3a	168.8	69.6	151.6	123.5	128.7	148.9	121.3	127.4
2b	169.8	69.6	146.4	123.3	142.7	130.3	125.5	128.5
3b	170.0	69.6	149.9	126.6	135.2	138.8	127.3	125.9

EXPERIMENTAL SECTION

Mps. are uncorrected. ^1H and ^{13}C nmr spectra were recorded on a Jeol FX-100FT spectrometer. Chemical shifts are given in ppm (δ, $CDCl_3$), using TMS as internal standard. Elemental analyses were done at the Microanalysis Laboratory of National Taiwan University. Isomer ratios (2a/3a and 2b/3b) were determined by HPLC (Shimadzu LC-4A) on a Lichrosorb SI-100 column with UV detection at 254 or 300 nm. The IR spectra (KBr pellets) were obtained with a Hitachi 360-50 spectrophotometer.

Preparation of 1,2-bis(Dibromomethyl)-4-nitrobenzene (1a).- 4-Nitro-o-xylene (15.1 g, 100 mmol) in 100 ml of chlorobenzene was placed in a two-necked flask equipped with a dropping funnel, and a reflux condenser attached to a sodium hydroxide trap for evolved hydrogen bromide. Liquid bromine (67.2 g, 420 mmol) in 50 ml of chlorobenzene was added dropwise, while the solution was irradiated with a 250W tungsten lamp. When the addition was completed (ca. 2 hrs), the reaction mixture was then cooled, washed successively with aqueous $NaHSO_3$ and distilled water, dried (anhydrous $MgSO_4$) and filtered. Removal of chlorobenzene under reduced pressure gave a yellowish precipitate which was recrystallized from CCl_4 and dried at 100° to afford 38.3 g (82%) of 1a as a pale yellow solid, mp. 127°.

Anal. Calcd. for $C_8H_5Br_4NO_2$: C, 20.59; H, 1.08; N, 3.00

Found: C, 20.60; H, 1.05; N, 3.02

The same procedure was used to prepare 3,4-bis(dibromomethyl)benzophenone (90% yield) isolated as a white solid, mp. 124°.

Anal. Calcd. for $C_{15}H_{10}Br_4O$: C, 34.26; H, 1.91. Found: C, 34.20; H, 1.90

Hydrolysis of 1,2-bis(Dibromomethyl)-4-nitrobenzene (1a).- Finely powdered 1,2-bis(dibromomethyl)-4-nitrobenzene (11.5 g, 24.6 mmol) was added to 30 ml of 95% sulfuric acid in a 250 ml round-bottom flask, equipped with distillation head, capillary ebullition tube and a receiver for vacuum distillation. The reactants were throughly mixed by means of a magnetic stirrer.Vacuum was applied and a stream of air was passed through the capillary tube to facilitate the rapid removal of hydrogen bromide. The flask was first heated in an oil bath to 70° and when gas evolution became less vigorous, the temperature was gradually increased to 110°. The reaction was completed when a clear solution was obtained, and gas evolution had ceased. After cooling, the contents were poured on to 100 g of crushed ice. The precipitate was collected, washed with water and dried at 100°. Chromatography of the crude product on silica gel, using $CHCl_3$-CCl_4 (1:3 by volume) as eluent gave 5- and 6-nitrophthalides, respectively.

The same procedure was used to hydrolyze 3,4-bis(dibromomethyl)benzophenone; 5- and 6- benzoylphthalides were separated from the crude product by silica gel chromatography using benzene as eluent.

Anal. Calcd. $C_{15}H_{10}O_3$ (for 2b): C, 75.62; H, 4.23. Found: C, 75.40; H, 4.19

Anal. Calcd. $C_{15}H_{10}O_3$ (for 3b): C, 75.62; H, 4.23. Found: C, 75.55; H, 4.16

The yields and the physical constants of compounds (2a,b and 3a,b) are listed in Table I.

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SYNTHESIS OF 3-QUINUCLIDINYL BENZILATE DERIVATIVES

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3-Quinuclidinyl benzilate (QNB) has been shown to be an effective muscarinic antagonist.[1] Radioiodinated analogs of QNB have been used effectively for myocardial imaging.[2] Generally, the radioiodinated QNB derivatives are obtained in low yield, by direct electrophilic iodination of 3-quinuclidinyl benzilate[3] or by halogen exchange reactions.[4] We have developed effective routes to 4-bromo- and 4-iodo analogs of QNB. These agents can be used to prepare the