A NEW SYNTHESIS OF PHTHALIDES THROUGH $\beta\text{-}scission$ of benzocyclobutenol hypoiodites 1

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Summary—A simple new method for the synthesis of phthalides and their 3alkyl and 3,3'-spiroalkyl derivatives including $(\underline{+})$ -3-butylphthalide, a racemic form of a constituent of celery oil, through the β -scission of alkoxyl radicals generated from hypoiodites of benzocyclobutenols by the photolysis, is described.

Phthalides have recently attracted considerable attention as valuable intermediates for the annelation of aromatic rings in the synthesis of triand tetracyclic aromatic natural products such as anthracycline antibiotics.² Several substituted phthalides have also been found in nature.³

In this communication, we wish to report a simple and novel method for the synthesis of phthalides 4 and their 3-alkyl and 3,3'-spiroalkyl derivatives.

The method for the preparation of phthalides consists simply of the preparation of 1-ethylbenzocyclobutenols caused by the reaction of appropriate benzocyclobutenones⁵ with ethylmagnesium bromide and the photolysis of their hypoiodites in benzene, as outlined in Scheme 1.

Typically, irradiation of 1-ethylbenzocyclobutenol (2a) in benzene containing mercury(II) oxide and iodine (3 equiv. each) with a 100-W high pressure Hg arc through a Pyrex filter at room temperature gave phthalide (3a) in a 41% yield. 7-Chloro (3b), 7-methoxy (3c)⁶ and 6,7-dimethoxyphthalide (3d) (meconin)^{3a} were prepared from the corresponding cyclobutenols (2b), (2c), and (2d) derived analogously from cyclobutenones (1b), (1c), and (1d) in 54-67% yields.

The method for the synthesis of 3-substituted phthalides, on the other hand, consists of the photolysis of the hypoiodites of catacondensed benzocyclobutanols; it gives 3-(ω -iodoalkyl)phthalides and their reduction with tributyltin hydride to 3-alkylphthalides or cyclization with a base to 3spiroalkylphthalides, as outlined in Scheme 2. Typically, the photolysis of tricyclo[6.4.0.0^{2,7}]dodeca-1(12),8,10-trien-7-ol (4a), after Andriux and Plat,⁷ in benzene under the same conditions as for the photolysis of the hypoiodite of 1-ethylbenzocyclobutenol (2a) gave 3-(ω -iodobutyl)phthalide (5a)⁸ in a 61% yield. Reduction of 5a with tributyltin hydride in benzene under reflux gave (<u>+</u>)-3-butylphthalide (6a), a racemic form of a constituent of celery,^{3c} in an 87% yield. On the other hand, with lithium diiopropylamide in THF-HMPA at

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Scheme 2.

-78°C for 30 min led to the formation of 3,3'-spirophthalide 7a in a 67% yield. Similarly, we were able to synthesize 3-pentylphthalide (6b) and 3,3'-spiropentylphthalide 7b from tricyclo[7.4.0.0^{2,8}]trideca-1(12),9,11-trien-8-ol (4b) through 3-(ω -iodopentyl)phthalide (5b), as outlined in Scheme 2.

The pathways that led to the formation of phthalides (3a-3d) and $3-(\omega-iodoalkyl)$ phthalides (5a) and (5b) in the present synthesis are outlined in Schemes 3 and 4. These pathways are parallel to those we have recently reported which lead to the formation of iodo formates in the photolysis of hypoiodites of steroidal cyclic alcohols.⁹ Thus, irradiation of the hypoiodite (A) of benzocyclobutenols generates a stabilized benzyl radical (C) <u>via</u> an alkoxyl radical (B). An intramolecular combination of the carbonyl oxygen and the carbon-centred radical of (C) affords a cyclic radical (D) which reacts





Scheme 4.

with iodine oxide or \cdot OI to generate a second hypoiodite (E). The second β scission of alkoxyl radical (F) generated from hypoiodite (E) under the experimental conditions gives phthalides 3a-3d and 3-substituted phthalides 5a and 5b. We were, in fact, able to isolate hemiacetal (G, n=1, R=H) when the photolysis of 4a was discontinued at an early stage of the reaction.

The application of this novel method for the synthesis of some biologically active natural products is under investigation and will be reported at a later date.

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