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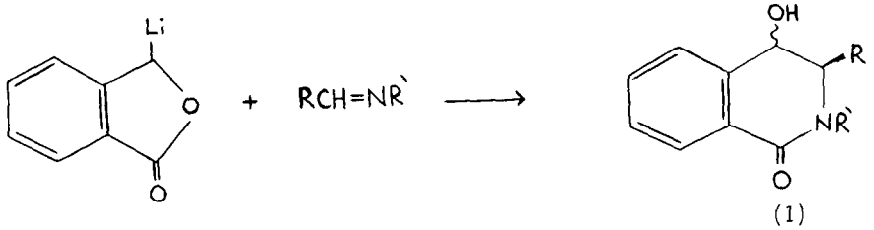
DECARBOXYLATION OF PHTHALIDECARBOXYLIC ACIDS IN THE PRESENCE OF IMINES - A FACILE ROUTE TO ISOINDOLO[1,2-b][3]BENZAZEPIN-5-ONES AND PHTHALIDEISOQUINOLINES

John Chiefari, Wit Janowski, and Rolf Prager*
School of Physical Sciences, Flinders University, Bedford Park, South Australia, 5042.

Abstract: In aprotic solvents, or in the absence of any solvent, phthalidecarboxylic acids decarboxylate in the presence of imines at 130° to form 3-alkyl-3-hydroxyisoindolones or their dehydration products. In acetic anhydride as solvent the products obtained are acetylated aminoalkylphthalides. The reactions are used to synthesise isoindolo[1,2-b][3]benzazepin-5-ones and phthalideisoquinoline alkaloids.

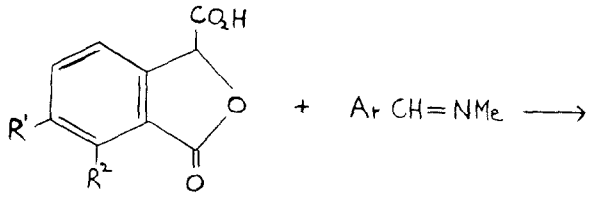
We have noted that the ease of decarboxylation of phthalidecarboxylic acids is markedly increased in the presence of various electrophiles,[1-3] and that the phthalide moiety is alkylated in the process. We now report our findings when the electrophile is an imine. Our work is complementary to that of Sammes[4] and MacLean[5], who have added phthalidyl anions to imines and obtained 4-hydroxyisoquinolinones (1).



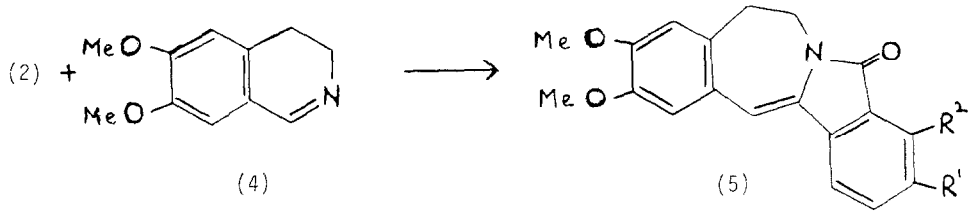
(1)

In aprotic solvents, or preferably without any solvent, phthalidecarboxylic acids (2) decarboxylate readily at 130° over 10 min in the presence of imines, the major products being the 3-alkyl-3-hydroxyisoindolone (3), but dehydration occurs when longer reaction times are employed. Some compounds prepared by this method are shown in Table 1 and below. When the imine was the dihydroisoquinoline (4), the product was the isoindolo[1,2-b][3]benzazepin-5-one (5). This ring system is of interest as a degradation product of protoberberine and papaverrubine alkaloids,[7-8] as a potential synthetic precursor of the rhoeadine alkaloids,[9] and has recently been shown to occur naturally in chilenine[10] and lennoxamine[11]. Although the yields of (5) are low ($R^1 = R^2 = OMe$, 50%; $R^1 = R^2 = H$, 35%), they compare more

than favourably in overall yield and directness with other available procedures.[9]



(2) (3)

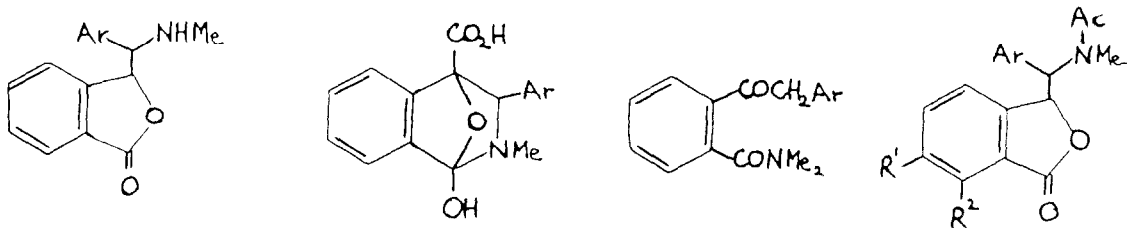


(4) (5)

Table 1. Preparation of Isoindolones (3)[6]

R^1	R^2	Ar	m.p. lit.	Yield %
H	H	C_6H_5	164° : 165-7°[14]	75
H	H	3,4-$(OMe)_2C_6H_3$	152-4°	80
OMe	H	3,4-$(OMe)_2C_6H_3$	175°	50

In contrast to the reaction of the phthalidyl anion studied by Sammes and MacLean, the aminoalkylphthalide (6) does not appear to be an intermediate to (3), as (6) is not converted to (3) under acidic, neutral or basic conditions. Evidence gained from a study of the decarboxylation of 3-alkyl and 3-deuterated phthalidecarboxylic acids suggests that decarboxylation follows a prior [4+2] cyclisation, the most likely intermediate being (7).



(6) (7) (8) (9)

When the potassium salts of the acids (2) are heated with an imine methiodide for 10 min in dimethylsulfoxide at 135°, the product is the benzamide (8), presumably formed by a pathway similar to that for (3).

When acetic anhydride is used as solvent, decarboxylation-alkylation of the acid is again rapid, but the products obtained in good yields (Table 2) are the aminoalkylphthalides as acetamides (9). The erythro and threo isomers are separable by chromatography. With the imine (4), which gives rise to phthalideisoquinolines, the ratio erythro:threo is of the order of 6, which is pleasing as only the erythro isomers show significant biological activity.[12] Hydrolysis of the acetamides could be achieved either by acidic hydrolysis[13] or by base, the latter conditions resulting largely in cyclisation of the erythro isomer to the trans isoquinolinone (1), [14-15] the threo isomer giving the aminoalkylphthalide.

Table 2. Preparation of Aminoalkylphthalide Acetamides (9)

R^1	R^2	Imine	Yield %
H	H	benzylidenemethylamine	95
H	H	3,4-$(OMe)_2$-benzylidenemethylamine	88
OMe	H	3,4-OCH_2O-benzylidenemethylamine	92
OMe	H	3,4-$(OMe)_2$-benzylidenemethylamine	95
H	H	(4)	35
OMe	OMe	(4)	50

Thus reaction of (4) with (2,R^1=R^2=OMe) gave N-acetyl norcordrastine (35%), which was hydrolysed to norcordrastine, identical with the product synthesised previously, and converted to cordrastine with formic acid-formaldehyde.[17]

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14. 1h reflux with ethanolic KOH; longer reaction times cause both isomers to cyclise.[15]
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