A FACILE SYNTHESIS OF PHTHALIDEISOQUINOLINES BY DECARBOXYLATION OF PHTHALIDECARBOXYLATES IN THE PRESENCE OF IMINE METHIODIDES‡

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Abstract - Decarboxylation of potassium phthalide-3-carboxylates in the presence of acyclic imine methiodides in DMSO leads mainly to 2-acylbenzamides, but with 3,4-dihydroisoquinolinium methiodides, a one step synthesis of phthalideisoquinilines is achieved in moderate yields.

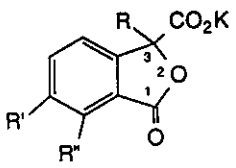
Phthalideisoquinoline alkaloids are of some interest because their convulsant properties are due to their specific inhibition of the neurotransmitter GABA in the brain.[1] Bicuculline (12), in particular, finds wide pharmacological use in defining the $GABA_A$ receptor, and in the search for anti-epileptic drugs.[2] Synthetic approaches to these compounds are numerous and diverse[3-6], but generally suffer the disadvantages of being multi step, with low overall yields.

In recent papers we have reported that phthalidecarboxylic acid decarboxylates more readily as a salt, and that when such decarboxylations are carried out in the presence of aldehydes[7] or conjugated ketones[8], addition products are readily isolated. Since we have recently reported that the acids undergo facile decarboxylation-alkylation in the presence of imines to give isoindolones,[9,10] we were interested to ascertain whether the use of the carboxylate offered any advantages.

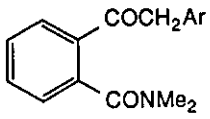
Potassium phthalidecarboxylate (1) did not react with imines, although decarboxylation to phthalide occurred. However, with the more electrophilic imine methiodide, decarboxylation was complete in fifteen minutes at 130°C in dimethyl sulfoxide, and the product with benzylidenemethylamine methiodide was the benzamide (2). In a similar way, the amide (3) was prepared. The minor product in these reactions was the aminobenzylphthalide (4). The 3-deuterated carboxylate (5) underwent the same reactions with no detectable isotope effect, and the 3-methyl carboxylate (6) failed to react totally, but did undergo decarboxylation. We therefore conclude that (1) undergoes rapid reversible deprotonation, and that the enolate (7) undergoes [4 + 2] cycloaddition to the intermediate (8)

‡Dedicated to Sir Derek Barton on the occasion of his seventieth birthday.

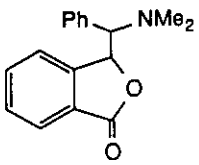
which leads to products.



	R	R'	R"
1	H	H	H
5	D	OMe	H
6	Me	OMe	H
14	H	OCH_2O	



2 Ar = C_6H_5
3 Ar = 3,4$(OMe)_2C_6H_3$



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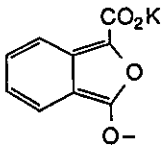

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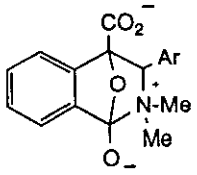

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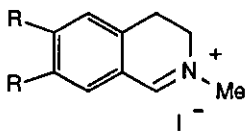
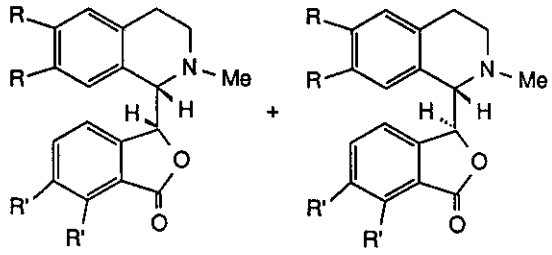
With dihydroisoquinolinium salts (9 and 10) reaction occurred within ten minutes at 130°C in dimethyl sulfoxide to give 50-70% yields of the diastereoisomeric phthalideisoquinolines (11-13), the stereoisomers of which are readily separable. No evidence for compounds analogous to the benzamides could be found.



9 R = OMe
10 R = OCH_2O



Erythro *Threo*

11 R = OMe R' = H
12 R = R' = OCH_2O
13 R = OMe R' = OCH_2O

EXPERIMENTAL

^{1}H Nmr spectra were measured in $CDCl_3$ on a Varian EM360A or a Jeol FX90 spectrometer. Mass spectra were determined on a Kratos MS25 BF instrument. Tlc separations were achieved using a Chromatotron on silica gel 60 PF_{254}. Elemental analyses were performed by the Australian Microanalytical Service, Melbourne, or the Canadian Microanalytical Services, New Westminster.

Potassium 3-Oxo-1,3-dihydroisobenzofuran-1-carboxylate (1) and Benzylidenemethylamine Methiodide

The potassium salt (1) (216 mg, 1 mmol) and the methiodide (260 mg, 1 mmol) were heated in dry DMSO (3 mL) for 10 min at 130°C. The cooled mixture was then extracted with 1M HCl (3 x 10 mL), which yielded 65 mg of a basic fraction shown by ^{1}H nmr analysis to contain equal quantities of two isomers. Direct crystallisation from ethanol yielded threo 3-[dimethylamino(phenyl)methyl]isobenzofuran-1(3H)-one (4) (35 mg), mp 161°C. Anal. Calc. for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.48; H, 6.32; N, 5.39. ν_{max} 1770, 1640, 1620 cm^{-1}. ^{1}H Nmr δ 2.50, s, 6H; 3.72, d, J 7 Hz, 1H; 7.2-7.8, m, 9H. The mother liquors contained largely the erythro isomer, but were not totally resolved.

The non-basic material on crystallisation from ether yielded N,N-dimethyl-2-(phenylacetyl)benzamide (2) (300 mg), mp 102-104°C (lit.[11] 101-104°C), identified by its spectral characteristics: ν_{max} 1690, 1635, 1580 cm^{-1}; ^{1}H nmr δ 2.75, 3.14, 2xs, 6H; 4.30, s, 2H; 7.5, m, 2H.

Potassium 5-Methoxy-3-oxo-1,3-dihydroisobenzofuran-1-carboxylate and 3,4-Dimethoxybenzylidenemethylamine Methiodide

The reagents (1 mmol) were reacted as above. The basic fraction (10 mg) was not further investigated. The neutral fraction was separated by tlc (CH_2Cl_2/ethyl acetate 1:1) to yield 6-methoxyisobenzofuran-1(3H)-one (50 mg) and N,N-dimethyl-2-(3,4-dimethoxyphenylacetyl)-5-methoxybenzamide (3) (150 mg), mp 146°C after recrystallisation from ether. Anal. Calc. for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.49; H, 6.40; N, 4.02. ν_{max} 1665, 1635, 1610, 1575 cm^{-1}. ^{1}H Nmr δ 2.75, 3.21, 2xs, 6H; 3.93, s, 9H; 4.23, s, 2H; 6.93, br s, 4H; 7.00, dd, J 9 Hz, 3 Hz, H-4; 8.02, d, J 8 Hz, H-3.

Potassium 5-Methoxy-1-methyl-3-oxo-1,3-dihydroisobenzofuran-1-carboxylate and 3,4-Methylenedioxybenzylidenemethylamine Methiodide

The reagents (1 mmol) were reacted as above. ^{1}H Nmr spectroscopy showed that only decarboxylation of the salt had occurred. 6-Methoxy-3-methylisobenzofuran-1(3H)-one was isolated quantiatively by tlc as a colourless oil. Calc. M^+ for $C_{10}H_{10}O_3$: 178.0630. Found: 178.0626. ν_{max} 1760, 1610 cm^{-1}. ^{1}H Nmr δ 1.60, d, J 7 Hz, 3H; 3.85, s, 3H; 5.49, q, J 7 Hz, 1H; 7.25, s, 3H.

3-(6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)isobenzofuran-1(3H)-one (11)

The potassium salt (1) and the methiodide of 6,7-dimethoxy-3,4-dihydroisoquinoline (0.6 mmol) were heated at 130-140°C for 20 min, as above. The crude product was separated by tlc ($CHCl_3$/MeOH, 9:1) to yield first the threo isomer (11), as pale yellow needles, mp 149-152°C (dec) (70 mg, 35%), and then the erythro isomer as a pale yellow oil (70 mg, 35%). Each was characterised by mass spectrometry, but did not give molecular ions. Calc. for $C_{12}H_{16}NO_2$ ($M^+ - C_8H_5O_2$): 206.1191. Found: 206.1181. ^{1}H Nmr threo δ 2.57-3.23, m, 4H; 2.70, s, 3H; 3.73, s, 3H; 3.85, s, 3H; 4.17, d, J 4 Hz, 1H; 5.77, d, J 4 Hz, 1H; 6.38, s, 1H; 6.73, s, 1H; 7.3-7.73, m, 4H. erythro δ 2.54, s, 3H; 2.4-2.98, m, 4H; 3.56, s, 3H; 3.82, s, 3H; 4.08, d, J 4 Hz, 1H; 5.73, d, J 4 Hz, 1H; 6.2, s, 1H; 6.6, s, 1H; 7.0-7.97, m, 4H.

3-(6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-6,7-methylenedioxyisobenzufuran-1(3H) one (13)

A mixture of the methiodide (9) and the salt (14) (1.54 mmol) was reacted as above. Tlc separation (acetone/CH_2Cl_2 1:1) afforded (±)-adlumine (13) (150 mg, 25%), mp 190°C (lit.[4] 187-189°C). ^{1}H Nmr δ 2.67, s, 3H; 2.57-3.33, m, 4H; 3.79, s, 3H; 3.84; s, 3H; 4.12, d, J 4 Hz, 1H; 5.73, d, J 4 Hz, 1H; 6.11, s, 2H; 6.46, s, 1H; 6.78, s, 1H; 6.78, s, 1H; 6.93, d, J 8 Hz, 1H; 7.21, d, J 8 Hz, 1H. The second band ($CHCl_3$/MeOH, 7:3) was identified as (±)-corlumine (13) (150 mg, 25%), mp 173-175°C (dec) (lit.[4] 175-176°C). Both isomers gave no molecular ion. Calc. for $C_{12}H_{16}NO_2$ ($M^+ - C_9H_5O_4$) : 206.1190. Found: 206.1181. ^{1}H Nmr δ 2.60, s, 3H; 2.47-3.28, m, 4H; 3.76, s, 3H; 4.07, s, 3H; 4.12, d, J 4 Hz, 1H; 5.70, d, J 4Hz, 1H; 6.20, s, 2H; 6.28, d, J 8 Hz, 1H; 6.48, s, 1H; 6.68, s, 1H; 7.0, d, J 8 Hz, 1H.

3-(2-Methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinolin-1-yl)-6,7-methylenedioxyisobenzofuran-1(3H)-one (12)

A mixture of the methiodide (10) and the potassium salt (14) (0.63 mmol) was treated as above. Preparative tlc ($CHCl_3$/MeOH, 9:1) yielded (±)-adlumidine (50 mg, 22%) as colourless crystals, mp 190-192°C dec. (lit.[12] 198°C). ^{1}H Nmr δ 2.17-2.67, m, 4H; 2.55, s, 3H; 4.05, d, J 4 Hz, 1H; 5.67, d, J 4 Hz, 1H; 5.88, s, 2H; 6.13, s, 2H; 6.45, s, 1H; 6.73, s, 1H; 6.9-7.13, m, 2H. The second band ($CHCl_3$/MeOH, 9:1) yielded (±)-bicuculline, mp 199-202°C (lit.[12] 215-216°C) (50 mg, 22%) as yellow crystals. ^{1}H Nmr δ 2.37-3.07, m, 4H; 2.57, s, 3H; 4.05, d, J 4 Hz, 1H; 5.6, d, J 4 Hz, 1H; 5.88, s, 2H; 6.03, s, 2H; 6.17, d, J 8 Hz; 1H; 6.4, s, 1H; 6.53, s, 1H; 6.9, d, J 8 Hz, 1H. Both isomers were characterised by their parent ion. Calc. for $C_{11}H_{12}NO_2$ ($M^+ - C_9H_5O_4$): 190.0855. Found 190.0868.

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