# Studies on $S_{RN}1$ Reactions. Part 6: [1] Synthesis of 3-Methyl Derivatives of the Alkaloids Thalactamine, Doryanine, and 6,7-Dimethoxy-*N*-methyl-1(2*H*)-isoquinolone

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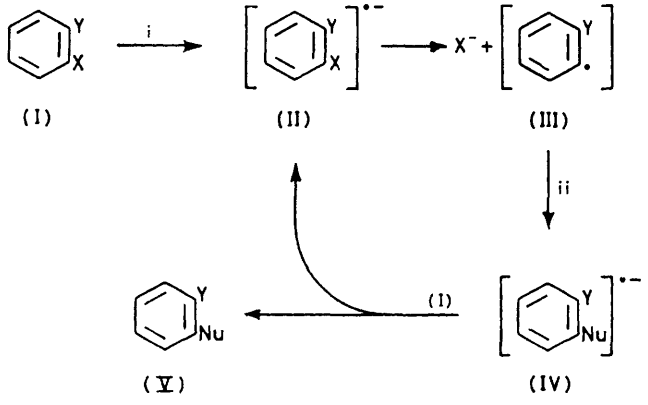
A new, short synthesis of the 3-methyl derivatives (3a—c) of the alkaloids thalactamine, doryanine, and 6,7-dimethoxy-*N*-methyl-1(2*H*)-isoquinolone, based upon our previous $S_{RN}1$ synthesis [1] of isocarbostyril [1-(2*H*)-isoquinolone] systems, is reported.

THE synthetic scope of the radical nucleophilic substitution reaction ($S_{RN}1$) is already broad [2] and was recently enhanced by the use of *ortho*-functionalized aryl halides ArXY (I) instead of simple aryl halides ArX. The advantage is that the nucleophile (ketone-derived enolate), being regiospecifically introduced at the site of the leaving group, can react in further synthetic step(s) with the *ortho*-functionality. This extended $S_{RN}1$ reaction involves *ortho*-functionalized intermediates (II), (III), and (IV) and has allowed straightforward synthesis of indoles,[3-5] azaindoles,[6] benzo[*b*]furans,[7]




X = leaving group (Br, I)
Y = Compatible group ($NH_2$, OMe, $CONH_2$) i $Nu^-$, *hν*; ii $Nu^-$

and simple isocarbostyrils [1(2*H*)-isoquinolones].[1] The synthesis of the title compounds was planned according to this method, using the appropriately substituted substrates (2a—c), (4a—c), or (6a), easily prepared for the corresponding commercially available acids (1a—c) (Scheme).

Using the acetone-derived enolate as the nucleophile, $S_{RN}1$ reactions on the substrates (2a—c), (4a—c), or (6a) should yield, respectively the desired alkaloid derivatives (3a—c) when Y = CONHMe, the 3-methylisocarbostyrils (5a—c) when Y = $CONH_2$, from which the alkaloid derivatives can be obtained after one more step, or the acid derivative (7a) when Y = $CO_2H$; compound (7a) is a formal precursor of the expected final product (3a). All three pathways were explored and the first one which requires only a one-pot reaction to give the desired 3-methyl derivatives, was attempted first.

## RESULTS

*Pathway A.*—From model studies [1] on simple *o*-bromo-*N*-methylbenzamides [*e.g.* (2); $R^1 = R^2 = R^3 = H$] we knew that it was possible to obtain the desired *N*-methylated isocarbostyril *via* an $S_{RN}1$ reaction, and that for an as yet unknown reason,† the reduction leading to various amounts of the *N*-methylbenzamides (9a—c) competes with the substitution. This was also the case with the substrates (2a—c) and the yield of (V) (not isolated) and subsequently those of (3a—c) (respectively 45, 60, and 40%) were only moderate, due to the undesired reduction.

*Pathway B.*—It was then obvious to us that a better yield of the isocarbostyrils (5a—c) could be obtained *via* the $S_{RN}1$ reaction and, provided an efficient and easy *N*-methylation method were available, pathway B would represent an efficient route to compounds (3a—c).

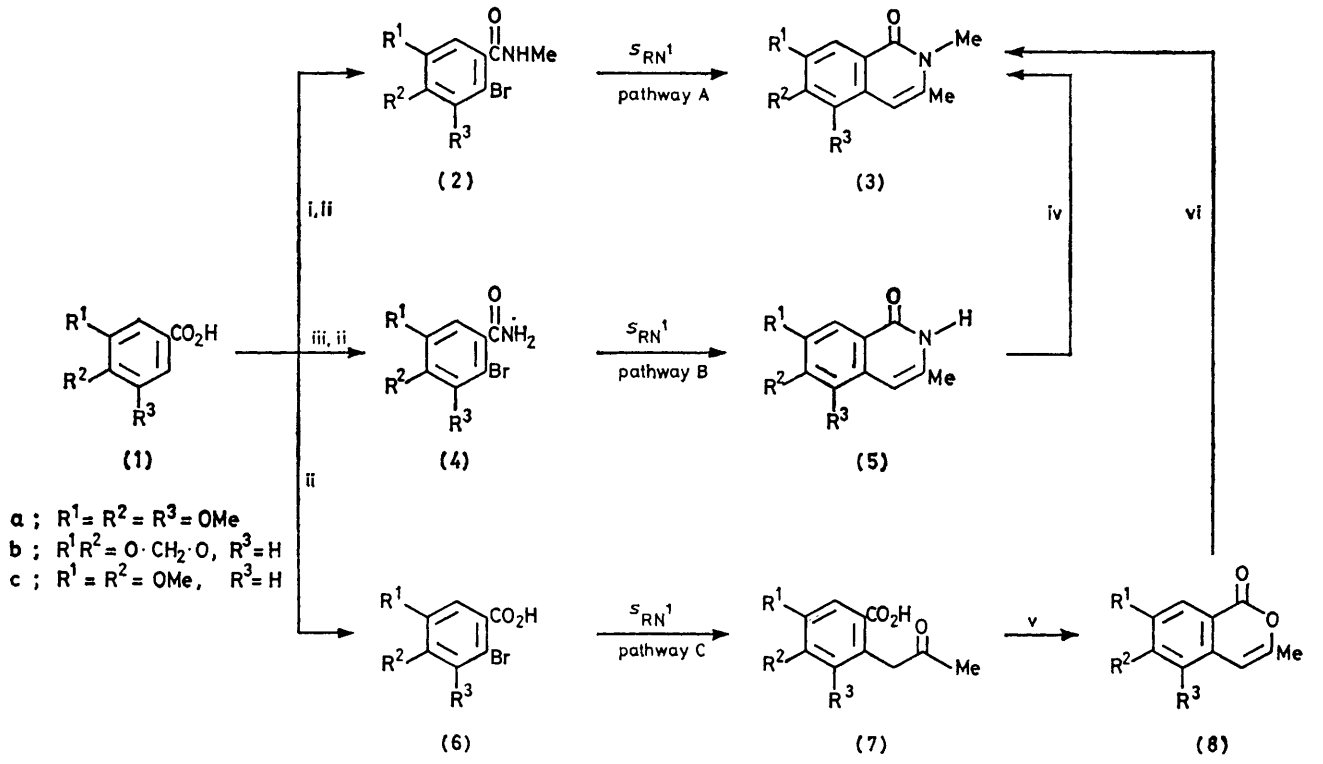
The $S_{RN}1$ reaction carried out on the *o*-bromobenzamides (Y = $CONH_2$) (4a—c) gave compounds (5a—c) in high yield (respectively 80, 70, and 75%). Furthermore, this reaction was faster [1 h for (4a—c), *vs.* 6, 1.3, and 4 h for (2a), (2b), and (2c), respectively]. A phase-transfer alkylation with MeBr gave the desired compounds (3a—c) in quantitative yield from (5a—c). Thus, pathway B turned out to be much better than the more direct pathway A, although one more step after the $S_{RN}1$ reaction was necessary.

*Pathway C.*—A third pathway can be considered, in which the $S_{RN}1$ reaction would be carried out directly on the *o*-halogeno-acid (6a) to give the desired *N*-methyl derivatives *via* the $S_{RN}1$ product (7a) and cyclization leading to (8a), an immediate precursor of (3a).

Only one example of an $S_{RN}1$ reaction using the *o*-bromobenzoic acid (10) and a ketone enolate has been reported.[8] We repeated this reaction with the acid (11) and obtained compound (12) which was treated with acid in a model reaction to give the isocoumarin (14) in high overall yield (80%). The *o*-bromo-acid (6a) was treated similarly and gave, after 2 h, compound (7a) (77%) contaminated with the acid (1a) (11%). Without further purification the crude mixture was treated with acid to give compound (8a). The replacement of the ring oxygen of the isocoumarin (8a) by N–R (here R = Me) is a classical reaction [9] which led to the required product (3a) (40%, not optimized overall yield).

Pathway C illustrates the synthetic utility of the free carboxylic function adjacent to the leaving group, but the

† We obtained *no* oxidized product ($ArCONH_2$ formed from $ArCONHCH_3$) which could support an intramolecular reduction as kindly suggested by a referee in analogy with results reported by M. F. Semmelhack and T. Bargar, *J. Org. Chem.*, 1977, **42**, 1481.




SCHEME *Reagents*: i, $MeNH_2$, 2,4,6-trichloro-*s*-triazine; ii, $Br_2$, $CHCl_3$–$H_2O$; iii, $NH_4OH$, 2,4,6-trichloro-*s*-triazine; iv, $[NBu^n_4]_2HSO_4$, NaOH, MeBr; v, $H^+$, benzene, 80 °C; vi, $MeNH_2$, dioxan, 100 °C

more tedious synthesis of compound (3a) requiring two steps after the $S_{RN}1$ reaction seemed to us to be less valuable than pathways A or B and was therefore not explored further with the analogous *o*-bromobenzoic acids (6b, c).

## DISCUSSION

The most efficient route to the derivatives (3a—c) is undoubtedly pathway B, but the two others are also of some interest. Using *o*-bromo-substituted secondary amides (Y = CONHR) or *o*-bromo-acids allows the synthesis of 3-methylisocarbostyril derivatives variously substituted on the ring-nitrogen atom by a substituent (aryl for instance) which could *not* be introduced *directly* on the 3-methylisocarbostyrils (5a—c).

The 3-methyl derivatives (3a—c) are easily converted into the natural alkaloids thalactamine (15), doryanine (16), and 6,7-dimethoxy-2-methyl-1(2*H*)-isoquinolone (17) by a smooth and high-yield reaction sequence.[10] These alkaloids could, in principle, have been obtained in a single $S_{RN}1$ reaction on the amides (2a—c) treated with the acetaldehyde-derived enolate. However, this nucleophile which worked moderately well with *o*-iodoaniline,[3,4] was found to be unsuitable when used with *o*-bromobenzamide since quantitative reduction to benzamide was the only observed reaction.

Only one natural product synthesis in which the crucial step was an $S_{RN}1$ reaction has been reported until now.[11] Our formal synthesis of the alkaloids (15), (16), and (17) shows that the $S_{RN}1$ reaction is a powerful tool for synthesis.

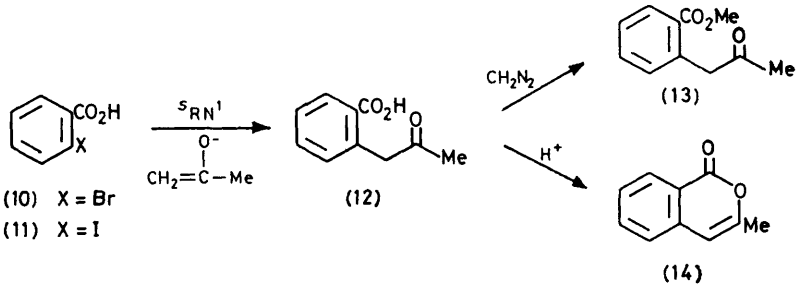
## EXPERIMENTAL

Melting points were determined on a Kofler apparatus. $^1H$ N.m.r. spectra were obtained on Varian T60 or Perkin-Elmer R12 instruments using $CDCl_3$ as solvent and $SiMe_4$ as internal standard. Mass spectra were recorded with an AEI MS9 spectrometer. Purifications were achieved by preparative t.l.c. on Kieselgel 60 GF 254 (Merck) plates. Development was with $CH_2Cl_2$–MeOH (5 to 10%); desorption was with acetone.

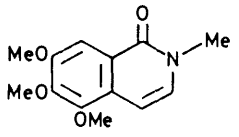
*Preparation of Starting Materials* (2a—c), (4a—c), and (6a).—Brominations were carried out using $Br_2$–$CHCl_3$–$H_2O$, according to literature methods,[12] on either the acid (1a) or the amides (primary or secondary) which were obtained from the acids (1b, c) by a recently reported method using 2,4,6-trichloro-*s*-triazine.[13] The following compounds were prepared. *2-Bromo-3,4,5-trimethoxy-N-methylbenzamide* (2a), m.p. 112—113 °C; *m/e* 305, 303 ($M^+$), 275, 273, 247, and 245; δ 2.95 (3 H, d), 3.85 (9 H, s), 6.35br (1 H, m), and 6.95 (1 H, s); *2-bromo-N-methyl-4,5-methylenedioxybenzamide* (2b), m.p. 163 °C; *m/e* 259 and 257 ($M^+$), 229, 227, 201, and 199; δ 2.95 (3 H, d), 6.0 (2 H, s), 6.20br (1 H, m), 6.97 (1 H, s), and 6.99 (1 H, s); *2-bromo-4,5-dimethoxy-N-methylbenzamide* (2c), m.p. 144—145 °C; *m/e* 275, 273 ($M^+$), 245, 243, 217, and 215; δ 3.0 (3 H, d), 3.90 (6 H, s), 6.40br (1 H, m), 6.95 (1 H, s), and 7.15 (1 H, s); 2-bromo-3,4,5-trimethoxybenzamide (4a), m.p. 166—167 °C (lit.,[14] 165.5—166.5 °C); 2-bromo-4,5-methylenedioxybenzamide (4b),[15] m.p. 163—165 °C; *m/e* 245, and 243 ($M^+$), 229, 227, 201, and 199; δ 6.0 (2 H, s), 6.8 (1 H, s), and 6.9 (1 H, s); *2-bromo-4,5-dimethoxybenzamide* (4c), m.p. 178 °C; *m/e* 261, 259 ($M^+$), 245, 243, 217, and 215; δ 3.90 (6 H, s), 6.9br (2 H, m), 7.0 (1 H, s), and 7.15

(1 H, s); 2-bromo-3,4,5-trimethoxybenzoic acid (6a), m.p. 148—150 °C (lit.,[12] 149—150 °C).

*General Procedure for the Preparation of Compounds* (3a—c), (5a—c), and (7a) *by the* $S_{RN}1$ *Reaction.*—To liquid ammonia (25 ml), prepared by condensing ammonia (gas) at −33 °C under argon in a three-necked flask fitted with a dry-ice condenser, was added acetone (4 mmol) and an equivalent amount of freshly sublimed potassium t-butoxide.




To the solution of the acetone enolate thus formed was added the appropriate substrate (2a—c), (4a—c), or (6a) (1 mmol) and the reaction mixture was irradiated (Rayonet RPR 204 apparatus from the S.O New England Ultraviolet Co. equipped with 4 RUL 3000 tubes). The reaction was monitored by taking aliquots which were analysed by t.l.c. [after methylation by diazomethane for (7a)] and quenched by addition of ammonium chloride (0.5 g) when all the substrate had reacted. The ammonia was then evaporated off and slightly acidified water (50 ml containing 2M HCl) (1 ml) was added. Extraction by $CH_2Cl_2$ (4 × 30 ml) followed by purification yielded the required compounds



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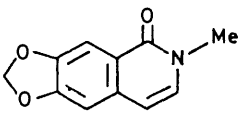

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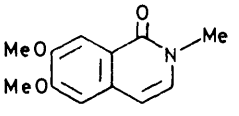

(17)

as follows. 5,6,7-Trimethoxy-2,3-dimethyl-1(2*H*)-isoquinolone (3-methylthalactamine) (3a), m.p.* 119—120 °C; *m/e* 263 ($M^+$); δ 2.40 (3 H, s), 3.57 (3 H, s), 3.97 (9 H, s), 6.57 (1 H, s), and 7.60 (1 H, s) (Found: C, 63.7; H, 6.45; N, 5.35. Calc. for $C_{14}H_{17}NO_4$: C, 63.88; H, 6.46; N, 5.32%). The yield from (2a) (irradiation time 6 h) was 45%, together with *N*-methyl-3,4,5-trimethoxybenzamide (9a) (30%); from (5a) (irradiation time 1 h) the yield was 80%. 2,3-Dimethyl-6,7-methylenedioxy-1(2*H*)-isoquinolone (3-methyldoryanine) (3b), m.p. 218 °C (lit.,[10] 215—216 °C); yield from (2b) (irrad. 1.30 h) was 60%, together with *N*-methyl-3,4-methylenedioxybenzamide [9b] (17%); yield from (5b) (irrad. 1 h) was 70%. 6,7-*Dimethoxy*-2,3-*dimethyl*-1(2H)-*isoquinolone* (3c), m.p. 179—182 °C; *m/e* 233 ($M^+$); δ 2.35 (3 H, s), 3.55 (3 H, s), 3.95 (6 H, s), 6.30 (1 H, s), 6.73 (1 H, s), and 7.66 (1 H, s) (Found: C, 66.9; H, 6.45; N, 5.9. $C_{13}H_{15}NO_3$ requires C, 66.95; H, 6.44; N, 6.00%). The yield from (2c) (irrad. 4 h) was 40%, together with 3,4-dimethoxy-*N*-methylbenzamide (9c) (46%); the yield from (5c) (irrad. 1 h) was 75%. 5,6,7-*Trimethoxy*-3-*methyl*-1(2H)-*isoquinolone* (5a), m.p. 198—200 °C; *m/e* 249 ($M^+$); δ 2.40 (3 H, s), 4.0 (9 H, s), 6.55 (1 H, s), and 7.60 (1 H, s). 3-*Methyl*-6,7-*methylenedioxy*-1(2H)-*isoquinolone* (5b), rather insoluble, purified only after methylation to (3b); δ 2.30 (3 H, s), 6.0 (2 H, s), 6.20 (1 H, s), 6.80 (1 H, s), and 7.60 (1 H, s). 6,7-*Dimethoxy*-3-*methyl*-1(2H)-*isoquinolone* (5c), m.p. 248 °C; *m/e* 219 ($M^+$); δ 2.40 (3 H, s), 3.98 (6 H, s), 6.20 (1 H, s), 6.80 (1 H, s), and 7.73 (1 H, s). 3,4,5-*Trimethoxy*-2-(2-*oxopropyl*)*benzoic acid* (7a), m.p. 212 °C; *m/e* 268 ($M^+$) and 225; δ 2.10 (3 H, s), 3.82—3.95 (11 H, m), and 7.45 (1 H, s); the yield from (6a) (irrad. 2 h) was 78%.

*Alkylation of Compounds* (5a—c).—The phase-transfer conditions described previously [16] were adapted as follows. The isoquinolone (5a, b, or c) (1 mmol) [or the crude product of the $S_{RN}1$ reaction from (4a, b, or c)] in benzene (3 ml) was strongly stirred with powdered NaOH (4 mmol), $K_2CO_3$ (1.5 mmol), and tetrabutylammonium hydrogen sulphate (0.1 mmol). After 10 min, MeBr (1.1 mmol) was added and stirring was continued at room temperature until the reaction was complete (1—2 h). Dichloromethane (30 ml) was added and the mixture was neutralized with diluted HCl. Further extraction with $CH_2Cl_2$ (2 × 30 ml) followed by classical work-up gave the expected *N*-alkylated product, identical with (3a, b, or c), respectively, in quantitative yield.

*Preparation of the Isocoumarin* (8a) *from* (7a).—A solution of the δ-keto-acid (7a) (134 mg) in benzene (8 ml) was treated with toluene-*p*-sulphonic acid (*ca.* 10 mg) and the mixture was refluxed overnight. Water was added and the product was extracted with ether and chromatographed on silica gel with $CH_2Cl_2$ as eluant to afford 5,6,7-*trimethoxy*-3-*methylisocoumarin* (8a) as an oil (90%); *m/e* 250 ($M^+$); δ 2.25 (3 H, s), 3.90 and 3.95 (9 H, 2 × s), 6.45br (1 H, s), and 7.44 (1 H, s) (Found: C, 62.2; H, 5.8. $C_{13}H_{14}O_5$ requires C, 62.39; H, 5.63%).

*Preparation of Compound* (3a) *from* (8a).—A solution of the isocoumarin (8a) (0.25 mmol) in dioxan (3 ml) was treated with 40% aqueous methylamine (2.5 mmol) and the mixture was warmed at 100 °C overnight. The dioxan

* Crystallised from methylene dichloride–methanol. Compound (3a) is identical (n.m.r. and mass spec.) with the sample m.p. 140—141 °C (from benzene–light petroleum) kindly provided by Dr. R. N. Usgaonkar.

was evaporated off and the product was purified by t.l.c. (silica gel). The product was identical with compound (3a); yield 60%.

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