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Articles

Development of Large-Scale Syntheses of Ropinirole in the Pursuit of a Manufacturing Process[1]

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Abstract:

Two plant syntheses of ropinirole {4-[2-(di-*n*-propylamino)-ethyl]-1,3-dihydro-2*H*-indolin-2-one hydrochloride, SK&F-101468-A} using the ferric chloride mediated cyclisation of *β*-nitrostyrenes to form 3-chlorooxindoles as the key step are described. The first synthesis suffered the severe limitation of the final-step chemistry being nonselective in the reaction between di-*n*-propylamine and the bromide precursor to ropinirole as both substitution and elimination pathways were promoted and by-product formation at a level of 40% resulted. This problem was rectified in the latter synthesis by the more selective reaction between di-*n*-propylamine and the sulfonate ester precursor promoting ropinirole formation to a level of 88%. This second synthesis is now used as the commercial route, and problems (and their solutions) identified during the development of this route are now described. The identification of novel by-products which enabled the Sommelet oxidation step to be optimised is also reported. A unimolecular decomposition mechanism during hydrolysis of the hexaminium salt to form the key benzaldehyde intermediate is proposed and substantiated with experimental data.

Ropinirole (**9**) is a potent non-ergot dopamine receptor agonist and has recently been marketed as a symptomatic treatment for Parkinson's disease. In a recent paper, the inadequacies of the medicinal chemistry route for preparing kilogram quantities of material, namely, high material costs and the length of synthesis, have been described.[2] In the search for more cost effective and efficient syntheses, we showed that preparation of 3-chlorooxindole derivatives *via* the ferric chloride−acetyl chloride mediated cyclisation of *β*-nitrostyrenes discovered by Royer could be utilised in the preparation of ropinirole.[3] The first synthesis using this chemistry is shown in Scheme 1.[4] The key nitrostyrene intermediate **4** was prepared in 80% yield *via* treatment of 2-(2-bromoethyl)benzaldehyde (**3**) with nitromethane anion in methanol, followed by an acidic quench in a two-pot procedure. Conversion of the nitrostyrene **4** to the 3-chlorooxindole **5** proceeded in 53% yield, and the quality of the product was assured by a single crystallisation from dichloromethane/petroleum ether (60:80) as it retained in solution the hydroxamic ester **6** and α-chlorooxime acetate **7**, known classes of by-product from this reaction. Although at first sight this yield appears modest, performing chemistry of this type is easily justified as the relatively complex oxindole nucleus is obtained in three processing steps using inexpensive and readily available starting materials and reagents. Furthermore, the cyclisation reaction offers no regiochemical issues, which were the main drawback of other syntheses we had considered. Reductive removal of the benzylic chlorine atom using catalytic transfer hydrogenation (CTH) was facile, providing the ropinirole precursor **8** in 95% yield.

This route was the first synthesis to be run on the pilot plant, producing 10 kg batches of ropinirole in 10% overall yield campaigns run on 250−750 L scale. Unfortunately, this route suffered two distinct drawbacks which precluded its use as a manufacturing process. The first of these problems centred on stage 1. Preparation of the benzaldehyde **3** was achieved *via* the photochemically initiated bromination of isochroman (**1**) based on a literature procedure.[5] This initially gives 1-bromoisochroman (**2**), which undergoes rearrangement at elevated temperatures in the presence of hydrogen bromide to give the benzaldehyde after purification *via* its crystalline sodium bisulfite addition complex. The main drawback to this reaction was that the plant yields (46%) were grossly inferior to laboratory values (85%). Although in both cases purification of the benzaldehyde was required for use in the next step, the lower plant yield was most disappointing. Originally the lower yield was believed to be a result of performing the bromination in inappropriate plant equipment. Unfortunately, improved yields were not obtained when specialised photochemical

(1) This paper was presented at the launch of *Organic Process Research & Development*, which was held in London on April 25, 1997.

(2) Hayler, J. D.; Howie, S. L. B.; Giles R. G.; Negus, A.; Oxley, P. W.; Walsgrove, T. C.; Walsh, S. E.; Dagger, R. E.; Fortunak, J. M.; Mastrocola, A. *J. Heterocycl. Chem*. **1995**, *32*, 875.

(3) Guillaumel, J.; Demerseman, P.; Clavel, J.-M.; Royer, R. *J. Heterocycl. Chem.* **1980**, *17*, 1531. Guillaumel, J.; Demerseman, P.; Clavel, J.-M.; Royer, R.; Platzer, N.; Brevard, C. *Tetrahedron* **1980**, *36*, 2459. Guillaumel, J.; Demerseman, P.; Clavel, J.-M.; Royer, R. *Tetrahedron Lett.* **1978**, 2011.

(4) Fortunak, J. M.; Giles, R. G.; Walsgrove, T. C. Eur. Pat. 0 300 614 A1, 1989; *Chem. Abstr.* **1989**, *110*, 212605r.

(5) Schmitz, E.; Rieche, A. *Chem. Ber.* **1956**, *89*, 1254. Schmitz, E. *Chem. Ber.* **1958**, *91*, 1133.

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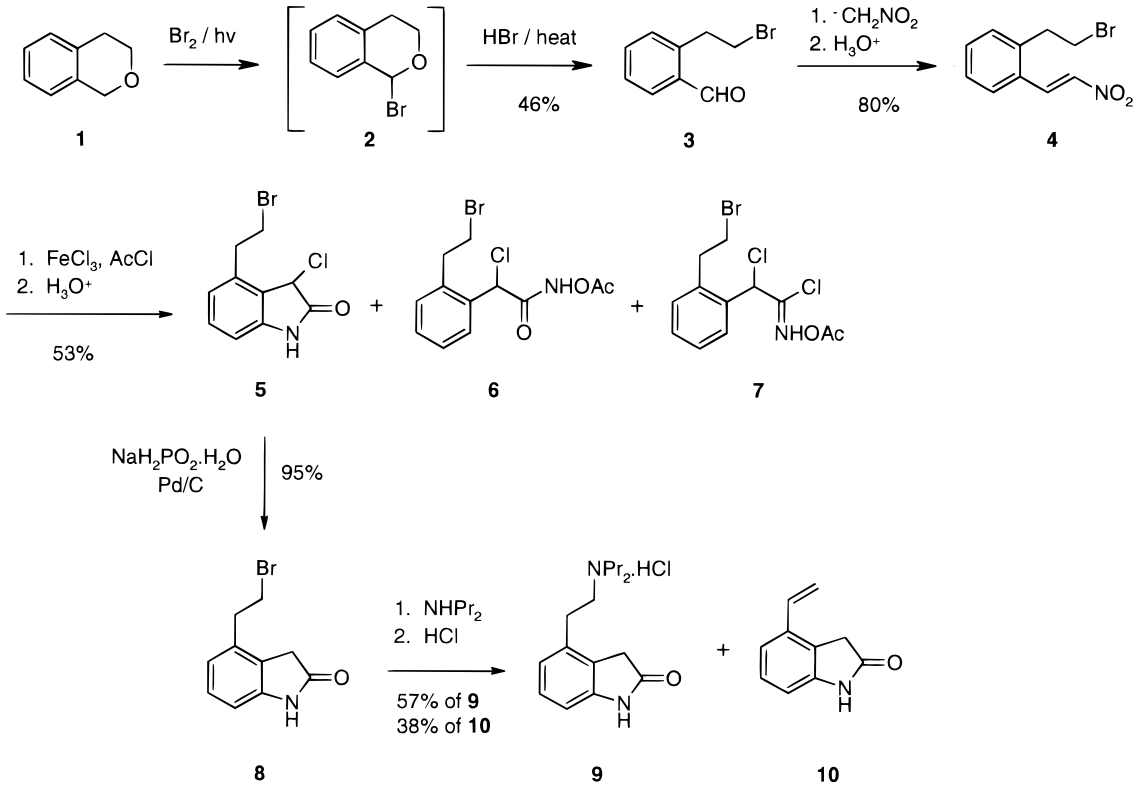
Scheme 1. **The first plant synthesis of ropinirole**



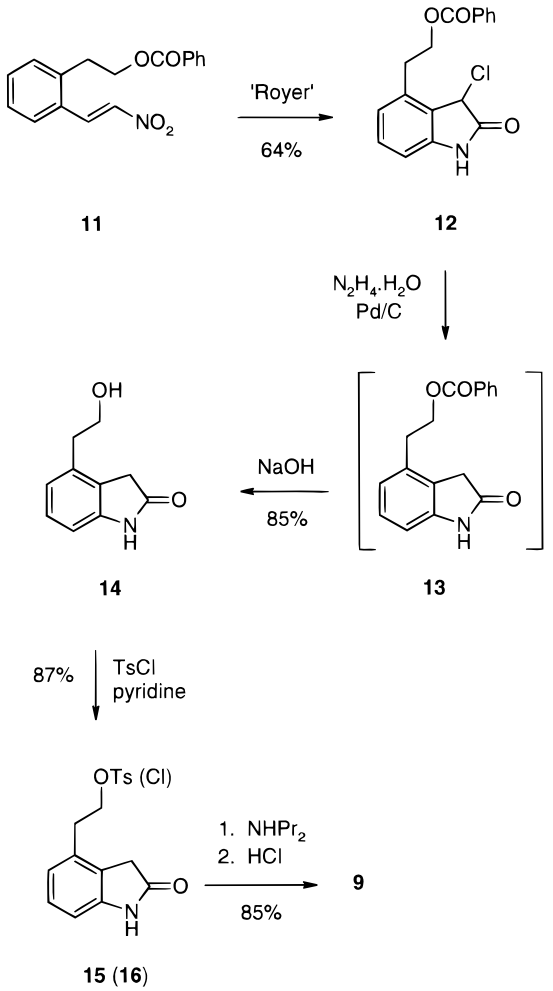
reactors were used which were deemed to provide conditions similar to those used in the laboratory. These results highlighted the prohibitive problem in generating bromine and isochroman radicals in concentrations comparable to those achieved under laboratory conditions and demonstrated that the 46% yield of **3** was unlikely to be improved.

The second drawback of this route was the inefficient final step. Reaction between the bromide **8** and di-*n*-propylamine in water gave ropinirole (**9**) in modest yield (57%), together with the styrene **10** as the major by-product (38%). Formation of ropinirole is a result of nucleophilic substitution of bromide by di-*n*-propylamine; however, the amine also assists in the accompanying styrene formation by acting as a base, resulting in the elimination of hydrogen bromide. Despite investigating the reaction in various solvents at different temperatures and concentrations, it was not possible to improve the yield of ropinirole. Due to these unavoidable inefficiencies of this synthesis, work was undertaken to discover an alternative.

We discovered that the reaction between di-*n*-propylamine and the tosylate **15** was highly selective, promoting the substitution reaction and improving the ropinirole to styrene ratio to 40:1, compared to 1.5:1 in the previous synthesis (Scheme 2). This ultimately resulted in the optimised process producing ropinirole in 85% isolated yield. The size and leaving group (LG) ability of the tosylate anion possibly explains the high selectivity for this reaction. Figure 1 represents the Newman projection for the antiperiplanar arrangement required for the elimination of HX to form styrene **10**, where X is the leaving group. In the halogen series, the better and larger LG facilitates the faster reaction and gives the worst ratio of **9** to **10**. Although the iodine atom is large, the energy barrier for the antiperiplanar configuration is still low enough to allow a significant degree of elimination reaction to take place. Bromine and chlorine, being poorer LGs than iodide, promote the substitution reaction pathway. Although the ratio of **9** to **10** looked promising using the chloride precursor **16**, it offered no advantage over the bromide **8** as only a 50% yield of ropinirole was obtained due to substantial product degradation occurring over the extensive reaction times required. The leaving group ability of the tosylate anion appeared to be similar to that of bromine, given the similar reaction times for **8** and **15**. However, with the tosylate group being much larger than the bromine atom, the degree of steric interaction between the oxindole ring and X in the antiperiplanar configuration required to eliminate HX increases. Therefore, the elimination pathway becomes energetically disfavoured for **15** over **8**, and a more selective (substitution) reaction with di-*n*-propylamine results.

The discovery of the highly selective substitution reaction of **15** meant that the alcohol **14** was now a key intermediate, and we quickly showed that the Royer cyclisation methodology could be utilised in its synthesis. The most appropriate β-nitrostyrene intermediate for the key step was shown to be the benzoate derivative **11**. Treatment of **11** under Royer's conditions gave the 3-chlorooxindole **12** in 64% yield in the optimised process. The crystallinity of this intermediate probably contributed to the relatively high yield. The reductive dechlorination of **12** using the CTH conditions of sodium hypophosphite hydrate in ethyl acetate/water from the previous route proved problematic in this case. The highly crystalline nature of the product ester **13** required the reaction mixture to be maintained at 70 °C to keep it in

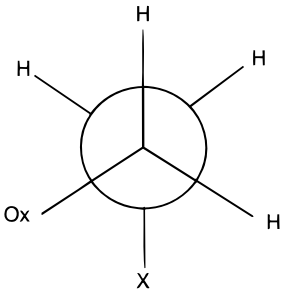
Scheme 2. **Later stages of the second plant synthesis of ropinirole**



solution. This made catalyst removal and separation of the water layer (containing the inorganic by-products from the hydrogen donor) difficult to perform. Subsequent work resulted in two improvements being made. First, hydrazine hydrate was chosen as the hydrogen donor, whose gaseous by-products eliminated the need for an aqueous workup. Second, it was shown that the alcohol **14** was more soluble than the ester **13** and so facilitated an easier removal of catalyst. Therefore, the hydrogenation and hydrolysis steps were combined to give **14** in 85% yield, thus removing one isolation and drying step. Preparation of the tosylate **15** from the alcohol using standard conditions proceeded in 87% isolated yield, particular care being taken over temperature control to avoid formation of the alkyl chloride **16**, formed *via* the reaction of the tosylate with chloride ion which is generated during this reaction. The chloride **16** did not react to give ropinirole during the short reaction times required for the tosylate and so represented lost yield.

The steps shown in Scheme 2 represent the latter steps of our manufacturing route.[6] The development of these steps was relatively straightforward and warrants no further mention here. However, the development of the preparation

(6) Giles, R. G.; Walsgrove, T. C. PCT Intl. Appl. WO 91/16306 A1, 1991; *Chem. Abstr.* **1992**, *116*, 106086m.

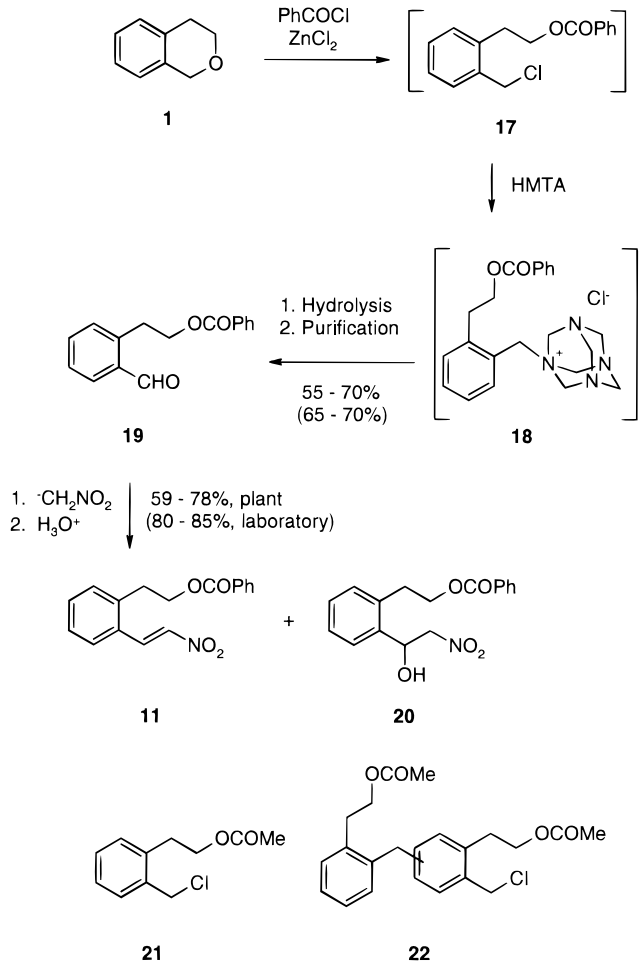


Compound	X	Reaction Time	9 : 10
-	I	< 15 mins	1 : 6
8	Br	2 hours	1.5 : 1
16	Cl	48 hours	6 : 1
15	OSO_2 - tol	1.5 hours	40 : 1

X = LG, Ox = oxindole ring.

Figure 1. **Ratio of ropinirole to styrene for a range of precursors containing various leaving groups (X).**

Scheme 3. **Preparation of the key nitrostyrene intermediate 11**



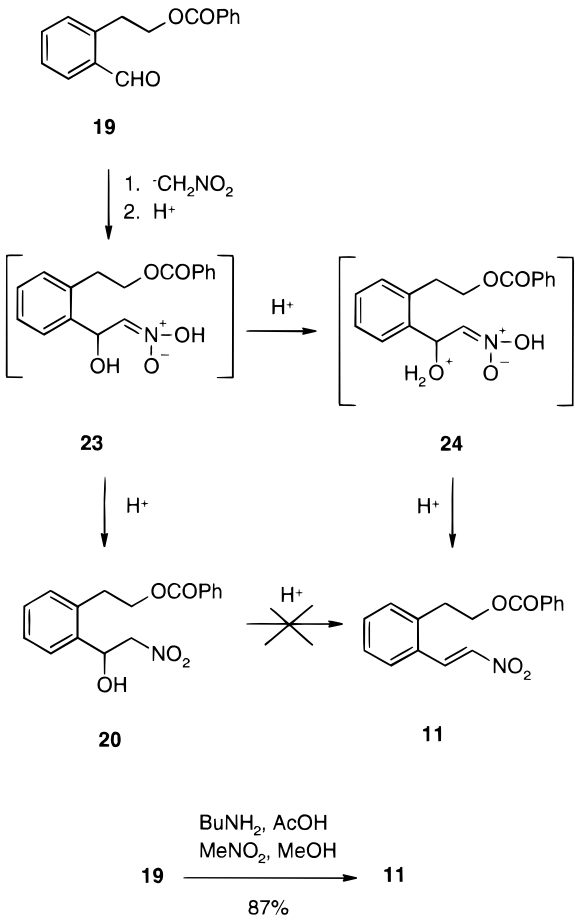
of the β-nitrostyrene **11** (Scheme 3) was less straightforward, and the following paragraphs describe the identification and solution of problems encountered during this work.

Treatment of isochroman with acetyl chloride in the presence of a stoichiometric amount of aluminium chloride was reported to give 2-(chloromethyl)phenethyl acetate (**21**) in 45% yield.[7] Compound **21** contained obvious attractive features in the hydroxyethyl side chain, together with an *o*-chloromethyl group, which could be oxidised to an aldehyde group. Investigations quickly showed that the low yield of **21** was attributable to its instability towards aluminium chloride resulting in its polymerisation. Evidence to support this was the isolation of the dimer **22** of undetermined regiochemistry, suggesting that **21** was reacting with itself in a Friedel−Crafts alkylation reaction. Using a much weaker Lewis acid such as zinc chloride improved the yield of **21** to greater than 95%, and a similar yield of 2-(chloromethyl)phenethyl benzoate (**17**) was achieved when acetyl chloride was replaced with benzoyl chloride . The preparation of the **17** was more desirable because ester exchange between this compound and sodium methoxide during the β-nitrostyrene preparation was minimised, which was not the case with the acetate **21**.

Kornblum oxidation of **17** in DMSO/sodium bicarbonate to give the benzaldehyde **19** proved a variable procedure in the laboratory, requiring elevated temperatures and producing a range of impurities whose formation could not be controlled. Therefore, our attention turned to the Sommelet oxidation. Reaction between **17** and hexamethylenetetramine (HMTA) in industrial methylated spirit (IMS) resulted in the quantitative formation of the hexaminium salt **18**. Replacement of IMS with aqueous acetic acid *via* a "put and take" distillation procedure resulted in the hydrolysis of the hexaminium salt to give the benzaldehyde **19**, which required purification *via* its sodium bisulfite addition complex. Fortunately, it was shown that the use of isolated chloromethyl compound **17** was not required since it did not enhance the purity of the crude benzaldehyde. Therefore, after formation of **17**, the reaction was water-quenched to remove zinc salts and the dichloromethane solution of **17** was used directly in the hexaminium salt preparation. The net result of this process was the one-stage conversion of isochroman to the crude benzaldehyde, and this formed the basis of the initial plant procedure to make **19**. Preparation of the β-nitrostyrene **11** was achieved under conditions similar to those used in the earlier plant synthesis. Scheme 3 shows the synthesis of **11** together with information on plant yields relative to laboratory values, and the reasons for the differences in these values are now discussed.

The preparation of the β-nitrostyrene **11** suffered three major drawbacks. First, it required purified benzaldehyde **19**. Although formation of the crude benzaldehyde was fairly straightforward, purification *via* its crystalline sodium bisulfite addition complex proved time-consuming due to problems in filtering the microcrystalline complex, which also resulted in physical losses in yield. Second, the β-nitrostyrene was prepared using a two-stage process which produced a water wet, low-melting solid, which required careful drying as the Royer chemistry needed stringently anhydrous conditions. Third, the preparation of the nitrostyrene resulted in the

Scheme 4. **Mechanism of nitro alcohol 20 formation and the modified preparation of the nitrostyrene 11**



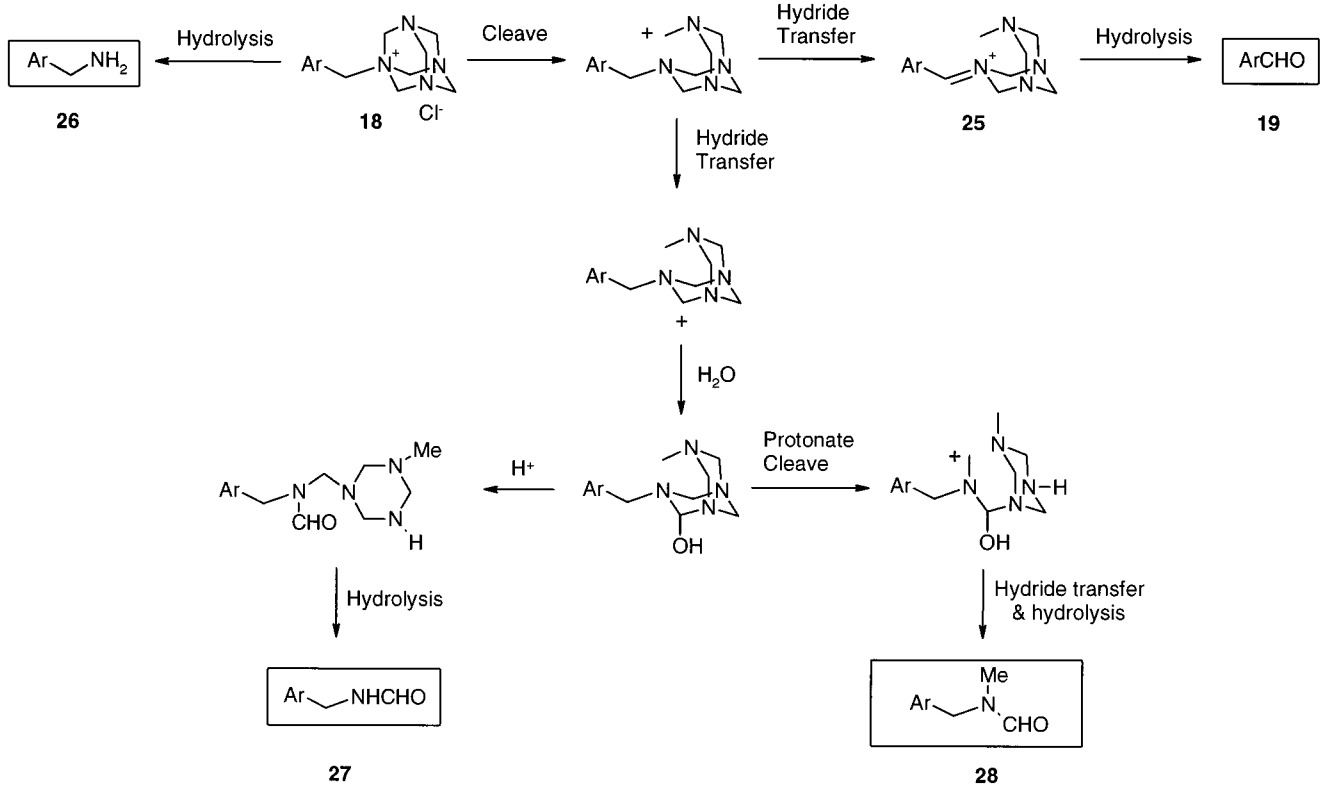
formation of a major by-product, the nitro alcohol **20**, sometimes at levels as high as 15%. This impurity did not form the chlorooxindole **12** in the next step and so represented lost yield. A proposal for nitro alcohol formation is shown (Scheme 4). Treatment of benzaldehyde **19** with nitromethane anion and addition of a proton is postulated to give the intermediate **23**, which upon further protonation has two possible pathways. Protonation on oxygen would lead to the formation of intermediate **24**, which after loss of water and a proton would form the nitrostyrene **11**. Protonation on carbon gives the nitro alcohol **20**. Despite extensive investigations, controlling nitro alcohol formation was not possible, and treatment of this impurity under more forcing acidic conditions did not result in nitrostyrene formation. Conversion of **20** to **11** required treatment with sodium methoxide and then aqueous acid. This was unattractive as a rework method as it still produced a water wet product.

To overcome these problems, we developed a variant of the MacDonald procedure for preparing β-nitrostyrenes from benzaldehydes under neutral conditions. In this reaction, the imine of the benzaldehyde is formed, which condenses with nitromethane, hence avoiding nitro alcohol formation.[8] Our reaction involved the treatment of **19** with nitromethane in the presence of equimolar quantities of *n*-butylamine and acetic acid, using methanol as solvent. This resulted in the

(7) Cologne, J. *Bull. Soc. Chim. Fr.* **1956**, 1337; *Chem. Abstr.* **1957**, *51*, 3581i.

(8) MacDonald, E.; Martin, R. T., *Tetrahedron Lett.* **1977**, 1317.

Scheme 5. **Proposed mechanism for the hydrolysis of the hexaminium salt**



crystallisation of **11** directly from the reaction mixture in 87% isolated yield using a single-pot process, to afford a methanol wet product which was easier to dry. Furthermore, the new preparation of **11** did not require purified benzaldehyde as input material and so use of the problematic bisulfite addition complex could now be omitted. To ensure that benzaldehyde of the required quality was routinely produced centred on two factors, a specific extractive workup procedure and optimisation of the hydrolysis of the hexaminium salt **18**, the latter of which is now discussed.

Investigation of the Sommelet oxidation resulted in the formamides **27** and **28** being identified as major by-products, and despite this reaction being well documented some 50 years ago (Scheme 5), products of this type had not been reported.[9] Previous papers suggested that hydrolysis of the hexaminium salt required excess hexamethylenetetramine, sometimes up to 4 equiv excess, to achieve good yields of benzaldehyde. It was believed that the hexaminium salt and HMTA degraded to the corresponding benzylamine and the primary imine of formaldehyde, respectively, and that these products underwent intermolecular hydrogen transfer ($ArCH_2NH_2 + CH_2{=}NH \rightarrow ArCH{=}NH + MeNH_2$) to form the primary imine of benzaldehyde, which was then hydrolysed. We believed this mechanism to be wrong because the yields of benzaldehyde **19** and formamide by-products **27** and **28** were constant over a range of HMTA used (1.2−4.0 molar equiv), and also when the hydrolysis step was performed under more dilute conditions (100−1000-fold), hence casting doubt on a bimolecular process. Furthermore, when 4 equiv of HMTA was used, the quality of isolated benzaldehyde was decreased to the extent that it could not be used directly in the nitrostyrene preparation. As a result of this work, 1.3 molar equiv of HMTA was found to be optimum.

Table 1. **Yields of benzaldehyde, secondary and tertiary formamides, and benzylamines from the hydrolysis of a series of hexaminium salts**

		yield (%)			
entry	Ar	ArCHO	**26**	**27**	**28**
1	phenyl	99	~1		
2	2-chlorophenyl	49	9	5	<1
3	2,6-dichlorophenyl	7	5	22	1
4	2,6-dimethylphenyl	45	34	10	1
5	2-[(benzoyloxy)ethyl]phenyl	80	1	5	3

As the yield of benzaldehyde was constant under a variety of conditions, we agreed with the theory of Blazevic that hydrolysis of the hexaminium salt occurred *via* a unimolecular mechanism, although this was not supported by experimental data.[10] We felt that this mechanism (Scheme 5) was further supported by the identification of the formamide by-products and by the fact that the yields of these relative to the benzaldehyde were also constant. To provide additional proof, we studied the formation and hydrolysis of the hexaminium salts derived from benzyl, 2-chlorobenzyl, 2,6-dichlorobenzyl, and 2,6-dimethylbenzyl chlorides (Table 1). We proposed that as the degree of ortho substitution increases, formation of the iminium salt intermediate **25** is suppressed, hence promoting alternative hydride transfer and hydrolysis processes to give formamide (**27** and **28)** and

(9) Angyal, S. J. *Org. React. (N.Y.)* **1954**, *8*, 197 and references therein.

(10) Blazevic, N.; Kolbah, D.; Belin, B.; Sunjic, V.; Kajfez, F. *Synthesis* **1979**, 161.

benzylamine (**26**). This was indeed observed as depicted in entries 1−3, although formation of the secondary formamide was favoured over formation of the tertiary by-product. It was also shown that electronic effects played a part in the pathway of this reaction. For example, the yield of 2,6-dimethylbenzaldehyde was much greater than for 2,6-dichlorobenzaldehyde. Despite strong steric interference by the flanking electron-donating methyl groups, their presence stabilised the iminium salt intermediate **25**, hence promoting benzaldehyde formation relative to the 2,6-dichloro case. During the course of this work, we were able to show that the acid strength was crucial to the yield and quality of benzaldehyde **19** and was optimum at 50% v/v aqueous acetic acid. This optimisation ultimately allowed us to dispense with the problematic bisulfite purification.

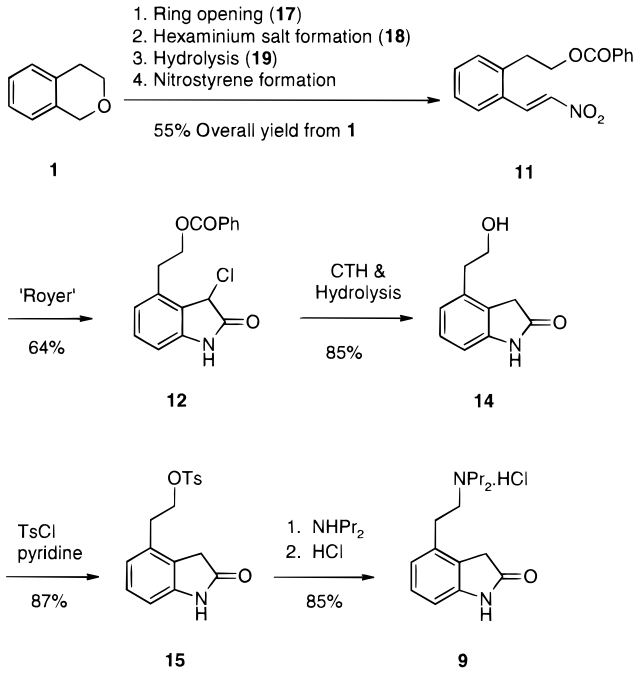
Development of the alternative β-nitrostyrene preparation and the optimised preparation and isolation of crude benzaldehyde meant that conversion of isochroman to the β-nitrostyrene could now be performed without isolation of intermediates. However, further improvement could still be made to this series of reactions. After formation of 2-(chloromethyl)phenethyl benzoate (**17**), an aqueous extraction procedure was required to remove zinc salts from the dichloromethane solution of the product, which was then used in the Sommelet reaction. This workup procedure was somewhat problematic due to the occasional formation of emulsions. Considering the mechanism of the isochroman ring opening reaction, we believed that it should be a catalytic process in zinc chloride. This hypothesis was shown to be correct in that performing the ring opening reaction in dichloromethane at reflux using 10 mol % zinc chloride gave **17** in comparable yield (95−98%) and purity compared to using 1.05 molar equiv at a temperature of 0−5 °C. This reduced level of zinc chloride was shown not to have a detrimental effect on the hexaminium salt formation, and so an aqueous workup for the preparation of **17** was no longer required. Instead, addition of IMS and HMTA to the reaction mixture and removal of dichloromethane by distillation results in complete hexaminium salt formation. This process change dramatically improved the ease in which the β-nitrostyrene was prepared and facilitated more robust processing.

In conclusion, we have extended the Royer oxindole methodology towards the synthesis of active pharmaceuticals and their intermediates and demonstrated its use for the first time, to our knowledge, in a plant environment. The single-stage preparation (four reactions) of the nitrostyrene **11** provides the firm basis for the second plant synthesis, which comprises five process stages (Scheme 6), all of which are robust and safe and can be run in nonspecialised plant equipment, and produces ropinirole with a 75% cost saving relative to the previous plant synthesis. It is because of these advantages that this second synthesis was selected for the commercial manufacture of ropinirole.

Experimental Section

Preparative details for the compounds listed below, together with full physical and spectroscopic data, have appeared in our previous paper.[2] For brevity, only those

Scheme 6. **Manufacturing route to ropinirole**



methods which differ markedly from those already reported are included in this section. For all compounds, details are given of the reaction scale and yields.

2-(2-Bromoethyl)benzaldehyde (3).[5] Isochroman (**1**) (30 kg, 224 mol) was converted to 2-(2-bromoethyl)benzaldehyde (**3**) (21.8 kg, 46%). The product was purified *via* its sodium metabisulphite addition complex.

2-(2-Bromoethyl)-β-nitrostyrene (4). 2-(2-Bromoethyl)-benzaldehyde (**3**) (18 kg, 84.5 mol) was converted to 2-(2-bromoethyl)-β-nitrostyrene (**4**) (17.3 kg, 80%).

4-(2-Bromoethyl)-3-chloro-1,3-dihydro-2*H*-indolin-2-one (5). 2-(2-Bromoethyl)-β-nitrostyrene (**4**) (15 kg, 59 mol) was converted to 4-(2-bromoethyl)-3-chloro-1,3-dihydro-2*H*-indolin-2-one (**5**) (8.5 kg, 53%).

4-(2-Bromoethyl)-1,3-dihydro-2*H*-indolin-2-one (8). 4-(2-Bromoethyl)-3-chloro-1,3-dihydro-2*H*-indolin-2-one (**5**) was converted to 4-(2-bromoethyl)-1,3-dihydro-2*H*-indolin-2-one (**8**) (13.3 kg, 95%).

4-[2-(Di-*n*-propylamino)ethyl]-1,3-dihydro-2*H*-indolin-2-one Hydrochloride (9) from the Bromide 8. 4-(2-Bromoethyl)-1,3-dihydro-2*H*-indolin-2-one (**8**) (12.5 kg. 52 mol) was converted to ropinirole hydrochloride (**9**) (8.8 kg, 57% yield).

2-[2-(Benzoyloxy)ethyl]-β-nitrostyrene (11). To a stirred solution of benzoyl chloride (115 kg, 822 mol) in CH_2Cl_2 (635 kg) was added zinc chloride (10.5 kg, 77 mol) at 25 °C, and the resulting mixture was stirred at 30−35 °C. Isochroman (**1**) (105 kg, 786 mol) was added, resulting in an exothermic reaction, and the reflux rate was controlled by the rate of addition. The resulting mixture was heated at reflux for a further 1 h. After cooling to 20−30 °C, 94% IMS (150 mL) and hexamethylenetetramine (166 kg, 1186 mol) were added to the reaction mixture, which was then heated at atmospheric pressure until 600 L of distillate had been collected. While the reaction mixture was maintained at reflux, a mixture of acetic acid (315 L) and water (315 L)

was added, and the reaction mixture was heated until 525 L of distillate had been collected at atmospheric pressure. The reaction mixture was cooled and extracted with *tert*-butyl methyl ether (810 L), and the organic layer was back-washed with 2 M sulphuric acid (574 L), 10% w/v aqueous sodium carbonate (2 × 525 L), and 26% w/v aqueous brine (525 L). The *tert*-butyl methyl ether extract was concentrated to a base temperature of 85 °C to give a mobile oil [2-formylphenethyl benzoate (**19**)], which was then dissolved in methanol (360 L). To the resulting solution were added, in quick succession and with care that the temperature did not exceed 30 °C, nitromethane (52 kg, 852 mol), acetic acid (16.9 kg, 282 mol), and *n*-butylamine (20.6 kg, 282 mol). The resulting mixture was stirred at 22 °C for 18 h to produce a thick suspension of 2-[2-(benzoyloxy)ethyl]-β-nitrostyrene, which was isolated in a centrifuge and washed with 2-propanol (520 L ml) total and dried to give 2-[2-(benzoyloxy)-ethyl]-β-nitrostyrene (**11**) (128 kg, 55% from isochroman).

4-[2-(Benzoyloxy)ethyl]-3-chloro-1,3-dihydro-2*H*-indolin-2-one (12). 2-[2-(Benzoyloxy)ethyl]-β-nitrostyrene (**11**) (100 kg, 336 mol) was converted to 4-[2-(benzoyloxy)ethyl]-3-chloro-1,3-dihydro-2*H*-indolin-2-one (**12**) (68 kg, 64%).

4-(2-Hydroxyethyl)-1,3-dihydro-2*H*-indolin-2-one (14). 4-[2-(Benzoyloxy)ethyl]-3-chloro-1,3-dihydro-2*H*-indolin-2-one (**12**) (100 kg, 317 mol) was converted to 4-(2-hydroxyethyl)-1,3-dihydro-2*H*-indolin-2-one (**14**) (48 kg, 85%).

2-(2-Oxo-1,3-dihydro-4-indolyl)ethyl *p*-Toluenesulphonate (15). 4-(2-Hydroxyethyl)-1,3-dihydro-2*H*-indolin-2-one (**14**) (55 kg, 310 mol) was converted to 2-(2-oxo-1,3-dihydro-4-indolyl)ethyl *p*-toluenesulphonate (**15**) (89.5 kg, 87%).

4-[2-(Di-*n*-propylamino)ethyl]-1,3-dihydro-2*H*-indolin-2-one Hydrochloride (9) from 2-(2-oxo-1,3-dihydro-4-indolyl)ethyl *p*-Toluenesulphonate (15). 2-(2-Oxo-1,3-dihydro-4-indolyl)ethyl *p*-toluenesulphonate (**15**) (82.8 kg, 250 mol) was converted to ropinirole hydrochloride (**9**) (63 kg, 85% yield).

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[⊗] Abstract published in *Advance ACS Abstracts,* December 1, 1997.