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Synthesis and Ring Cyclization–Expansion–Contraction Reactions of Some New 2,2-Disubstituted Indan-1,3-diones and Related Compounds

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We have found that the hydrochloride of 2-phenyl-2-[2-(2-piperidyl)ethyl]-4,5,6,7-tetrahydroindan-1,3-dione **1** possesses marked analgesic activity (100% inhibition referenced to codeine) and report, as part of an extensive synthetic program, the synthesis of 38 new and structurally related compounds.

Selective catalytic hydrogenation of the pyridine ring of 2-phenyl-2-[2-(2-pyridyl)ethyl]-indan-1,3-dione **2** yields the nine-membered nitrogen-containing heterocycle **6** by a novel ring cyclization–expansion reaction. The structural and functional group parameters required for this novel ring-expansion reaction have been extensively and thoroughly investigated through the synthesis of a series of structurally related compounds; principally by modification, substitution, and replacement of the various functionality contained within **2**.

In addition, we report the synthesis of a series of new 2-methyl-2-(ω-*N*-phthalimidoalkyl)-indan-1,3-diones **41**, **45**, and **53**, two of which, like the parent 2-phenyl substituted indan-1,3-dione **2**, also undergo a novel ring cyclization–expansion reaction to yield eight- and nine-membered nitrogen-containing rings. However, in these cases, further transannular reactions occur to produce the new 5,5- and 5,6-ring-fused nitrogen-containing heterocycles **44**, **48** and **51**, **52**. Hydrazinolysis of the third, 2-methyl-2-(4-*N*-phthalimidobutyl)-indan-1,3-dione yields the new azepine-containing ring structure **56** by direct cyclization.

Furthermore, some interesting and unexpected chemical properties of the final compounds, which include selective and non-selective pyridine-ring hydrogenations and a few unexpected side reactions, are described.

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Introduction

2-Substituted indan-1,3-diones are of pharmacological interest and importance since these are known to possess anti-inflammatory,[1] hypermetabolic,[2] anticoagulant,[3] uricosuric,[4] analgetic,[5] rodenticidal,[6] antibacterial,[7] bronchodilator,[8] and parasiticidal[9] properties. In the light of the above, and the fact that substituted indan-1,3-diones that also possess various nitrogen-containing functionalities have been relatively unexplored, led us to embark on an extensive synthetic program to investigate the chemistry and potential pharmacological activity of these new structures. Further, during the course of this project we synthesized and isolated the hydrochloride of 2-phenyl-2-[2-(2-piperidyl)ethyl]-4,5,6,7-tetrahydroindan-1,3-dione **1** (Fig. 1), which was found to possess marked analgesic activity (100% referenced to codeine).[10] This marked analgesic activity added further interest to the project, and focussed some of our synthetic endeavours towards related structures. (Note: we have/had no control over the decision of which compounds were pharmacologically tested, or over the limited results with which we were furnished.)

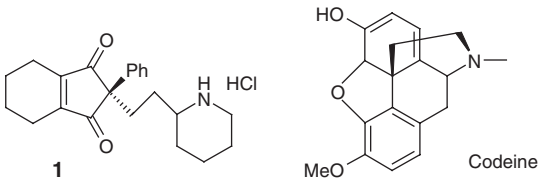

Fig. 1. The structures of compound **1** and codeine.

In addition, during the course of this project, we discovered that selective catalytic hydrogenation of the pyridine ring of 2-phenyl-2-[2-(2-pyridyl)ethyl]-indan-1,3-dione **2** yielded, via a 'one-step' novel ring cyclization–expansion reaction, a nine-membered nitrogen-containing heterocycle **6** in a relatively excellent 60% overall yield.[11] Further to the above mentioned biological activity of indan-1,3-diones, medium-sized nitrogen-containing rings, related in structure to **6**, are of importance since they are reported to exhibit

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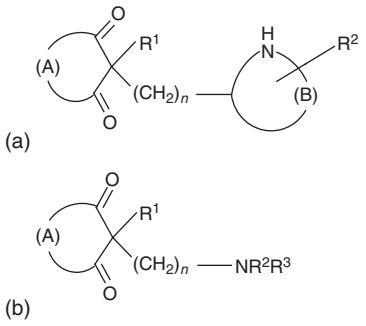


Fig. 2. Overview of the structural modifications detailed here.

sedative,[12,13] muscle relaxant,[12,13] anticonvulsant,[12,13] and marketed psychosedative[14–16] and tranquillizing[14–16] properties. The known biological activity of these structures was, therefore, an additional driving force to thoroughly investigate the scope of this potentially very useful, and relatively simple, 'one-pot' route to medium-sized rings. Furthermore, medium-sized rings are classically difficult to prepare, usually requiring multiple steps, and invariably associated with poor yields. Consequently, we extensively investigated the generality and applicability of this ring-expansion reaction to other structurally related compounds. This was achieved by dissection, modification, substitution, and replacement of the functionality associated with the parent structure **2**, and subsequent investigation of the reactivity of this introduced functionality, to see whether this affected the course and outcome of the above-mentioned ring-expansion-reaction sequence. The detailed structural modifications made are described in detail under the appropriate sections throughout this paper; however, a brief overview with specific reference to the general structures, depicted in Fig. 2, is given here. With reference to Fig. 2: (a) The degree of saturation contained within the indan-1,3-dione nucleus, –(A)–, was varied in order to investigate the effects of introducing partial and full saturation; (b) variations in the length of the alkyl linking chain, $-(CH_2)_n-$, for $n = 1$ and 2, were made, and an additional structure ($n = 1$) that possesses a 3-pyridyl nucleus, were investigated; (c) replacement of the pyridine ring (B) with a quinoline, with both fully unsaturated and partially saturated indan-1,3-dione nuclei, –(A)–, was investigated; (d) substitution of the pyridine ring with an alkyl group ($R^2 = 5$-ethyl) was achieved and investigated; (e) the size of the ring-containing the 1,3-dione functionality (A) was varied in order investigate the effects that a change in ring strain induces; and lastly (f) the substitution of $R^1 = Ph$ for an alkyl grouping ($R^1 = Me$) was investigated. With reference to Fig. 2b: (a) variation of the length of the alkyl linking chain $-(CH_2)_n-$, for $n = 2$ and 3 and $R^1 = Ph$, possessing both a partially saturated indan-1,3-dione nucleus, –(A)–, and terminal *N*-phthalimidoalkyl ($-NR^2R^3$) groups, was investigated, and finally (b) an investigation of the variation of the length of the alkyl linking chain $-(CH_2)_n-$, for $n = 2$, 3, and 4 with $R^1 = Me$, possessing both an indan-1,3-dione nucleus and terminal *N*-phthalimidoalkyl ($-NR^2R^3$), was made.

During the course of this synthetic program we noted some interesting reactivity and chemical properties of the synthesized target compounds: In particular, the expected selective catalytic hydrogenation of the pyridine portion of the quinoline ring of the indan-1,3-dione structure **15** was obtained. However, under identical hydrogenation conditions, the corresponding 1,2,3,4-tetrahydroindan-1,3-dione compound **17** afforded the unexpected selective hydrogenation of the benzene portion of the quinoline ring.

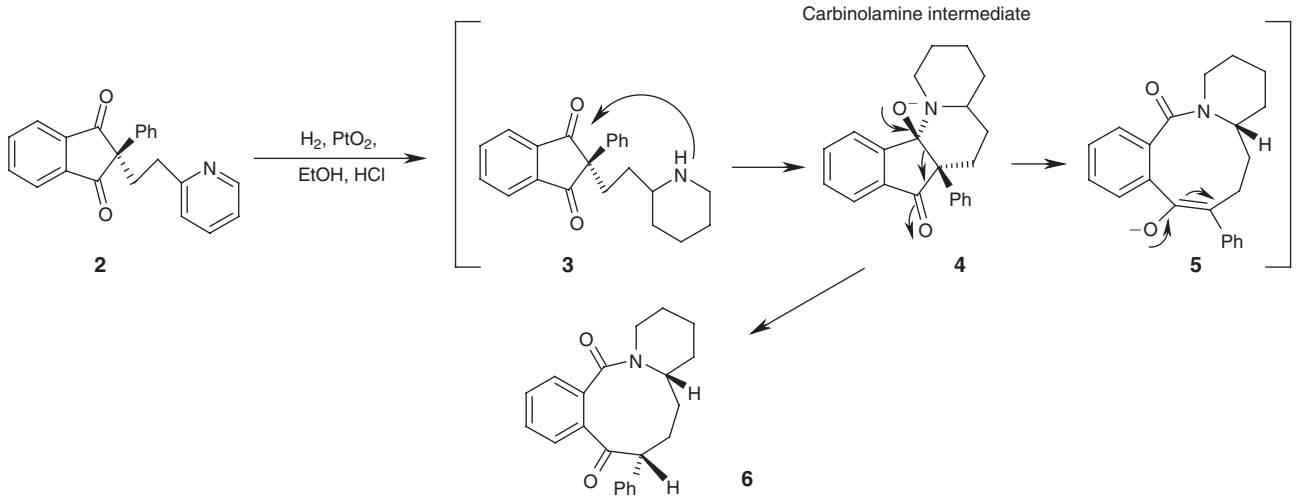
Some further synthetic modifications of the final ring structures were investigated, which produced en route some new chemical entities. Specifically, it was found that the isoindole **30** produced, on treatment with a hydride reagent, the new 5,6-fused nitrogen-bridgehead heterocycle **33**, the stereochemistry of which has been deduced. In addition, the nine-membered ring system **6**, when treated with sodium borohydride, underwent an unexpected hydride-induced transannular-contraction reaction (a lactam-to-lactone interchange) to afford the new lactone-containing compound **57**.

Results and Discussion

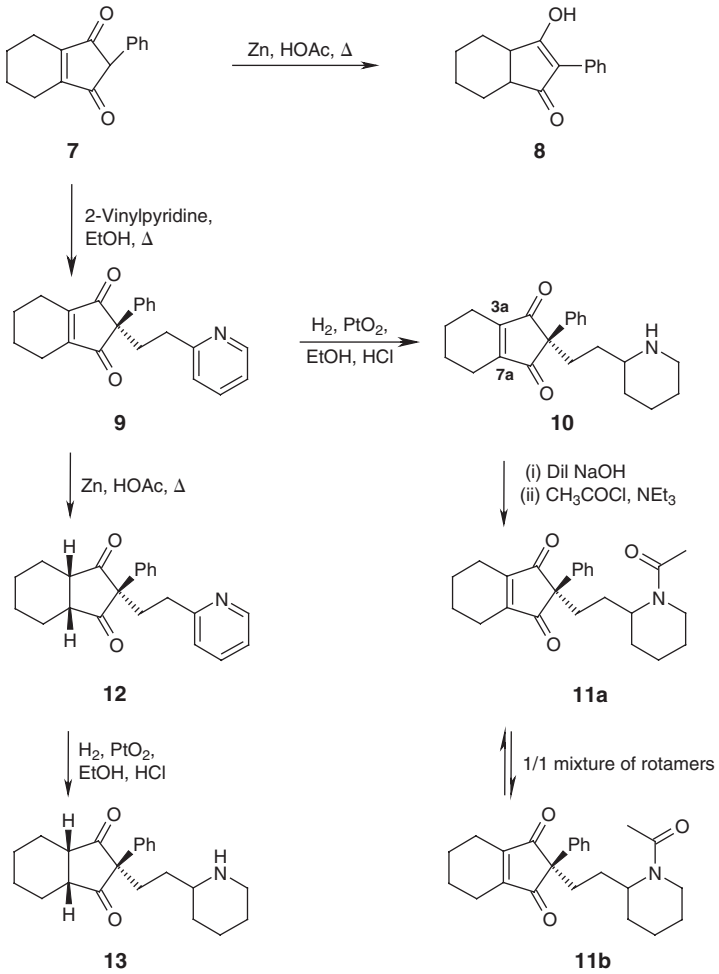
Synthesis of 2-Pyridyl and 2-Piperidyl-Containing Structures Possessing Tetrahydro- and Hexahydroindan-1,3-dione Nuclei. Selective Ene-1,4-dione and Pyridine Ring Reductions

Since we reported that the selectively catalytically reduced piperidyl variant of **2** underwent a novel ring cyclization–expansion reaction to a nine-membered ring (Scheme 1), we were interested to investigate whether this reaction sequence could be reproduced utilizing compounds possessing slightly different chemical functionality. Initially, we were interested in synthesizing compounds that contained small structural variations, i.e., the partially saturated **9** and corresponding fully saturated indan-containing system **12** (see Scheme 2). In addition, the marked analgesic activity of **1** offered a further reason for us to synthesize and explore structurally similar variants as possible candidates for pharmacological screening. Compound **7**[17] readily underwent a Michael-type addition to 2-vinyl pyridine, in an ethanol reflux, to yield 2-phenyl-2-[2-(2-pyridyl)ethyl]-4,5,6,7-tetrahydroindan-1,3-dione **9** in an excellent 84% yield.

Selective catalytic hydrogenation of the pyridine portion of this compound, in the presence of two equivalents of hydrochloric acid, gave the hydrochloride of 2-phenyl-2-[2-(2-piperidyl)ethyl]-4,5,6,7-tetrahydroindan-1,3-dione **10** (91%). Attempts to prepare the corresponding free piperidyl compound, by treatment with aqueous base, resulted in polymerization, presumably by intermolecular Michael-type additions of the resulting secondary amines to the activated 3*a*,7*a*-ene-dione functionality. High dilution basification of this compound followed by *N*-acetylation (access acetylchloride/triethylamine) allowed isolation and characterization by the *N*-acetamido derivative **11a**/**11b** (55%). Presumably, the *N*-acetylation reaction proceeds more rapidly than the competing intermolecular Michael-type polymerization, as a 55% yield of the amide **11a**/**11b** is obtained. (^{1}H NMR showed this to be a 1/1 mixture of its two amide rotamers at room temperature.)



Scheme 1.



Scheme 2.

In view of the instability of the above compound, we decided to investigate the hexahydroindan-1,3-dione-containing systems **12** and **13**. This was primarily to investigate exactly what functional groups and structural parameters were required in order for the novel ring cyclization–expansion reaction, typified by the conversion of **2** → **6**, to progress. It would also produce further analogues for pharmacological screening.

Initial synthesis of the hexahydroindan system **8** was achieved by a zinc reduction of the internal 3*a*,7*a* double bond of **7** to yield 2-phenyl-hexahydroindan-1,3-dione (Scheme 2).[17] Even with the use of a variety of catalysts

(sodium metal, crushed sodium or potassium hydroxide pellets), this would not, however, undergo a Michael-type addition with 2-vinyl pyridine. Since α,β-unsaturated ketones are reported to be reduced to saturated ketones using zinc dust in acetic acid,[18] this method was applied to **9** in the hope of obtaining selective reaction over other present functionalities, in particular, the possible problems associated with the dimerization of the pyridine nuclei through radical anion mechanisms, and keto-group reductions. Initial problems (polymer formation) were encountered in obtaining the required selectivity over other present functionalities. However, this was overcome by limiting the time of the reaction to 25 min to produce **12** (60%). Selective catalytic hydrogenation of the pyridine ring of **12**, using Adam's platinum oxide, yielded **13** (56%), which was deduced by ^{1}H NMR to possess a *cis*-ring fusion. This system did not undergo a ring cyclization–expansion reaction to a nine-membered ring-containing system. We believe this is probably due to a combination of the differing electronic, steric, and ring-strain effects,[19] relative to the fully unsaturated indan-1,3-dione system.

Synthesis of 2-Substituted Tetrahydroindan-1,3-diones Possessing Methylene Linkages to 2- and 3-Substituted Pyridine and Piperidine Rings

We were also interested in investigating a shorter pyridine/piperidine to indan-1,3-dione alkyl-linkage, i.e., the methylene-containing analogue **58** (see Table 1 and Accessory Materials). This was predominantly for two reasons: first, a methyl linking group between the 2-piperidyl and indan nuclei would add structural rigidity to the overall molecule, which is particularly important when considering potential drug candidates and their specificity of interaction with receptor sites in the human body; and second, to investigate whether the overall structure that possessed the shorter methyl-linkage would undergo the novel ring cyclization–expansion reaction sequence, in comparision with structure **2**. The latter would be of interest, particularly when considering that the syntheses of medium-sized rings by the more classical direct-cyclization routes are generally difficult to achieve, require multiple steps, and are usually accompanied by poor yields. It was also of interest since it offered the potential to further extend the novel ring cyclization–expansion reaction to produce eight-membered medium-sized nitrogen-containing heterocyclic rings in potentially good overall yields.

The synthesis of **58** was achieved via the initial synthesis of 2-picolyl chloride hydrochloride, derived from 2-pyridylcarbinol,[20] and treatment of this with the sodio-derivative of 2-phenyl-4,5,6,7-tetrahydroindan-1,3-dione. (Attempts to alkylate with the corresponding picolyl bromides failed. These proved to be too reactive and underwent total self-quaternization to form a solid red polymer.) Selective catalytic hydrogenation of the pyridine ring of **58**, in the presence of hydrochloric acid, yielded the hydrochloride of **59** (see Accessory Materials). However, production of the free base did not produce the expected eight-membered ring. This is probably due to the strain of the required 5-membered ring transitional carbinolamine intermediate, comparable with **4**, and due to the strong preference for the methylindan-nucleus to adopt an equatorial conformation to the piperidine ring. Both these factors make attack of the secondary amine at the keto-groups energetically and sterically unfavourable, which precludes the formation of the expected eight-membered ring.

To produce further variants for pharmacological screening, and to retain the more rigid methylene linkage, we also synthesized the 3-pyridyl-substituted analogue **60**, since positioning, and thus biological availability, of the nitrogen atom can affect biological availability, and hence activity. This compound (Accessory Materials) was synthesized using a similar procedure to that of the 2-pyridyl-substituted analogue. However, yields were poor, probably due to the lower electrophilicity at the 3-position. In addition, quantities of a side product, characterized as **14** (Fig. 3) were obtained, which indicated a Michael-type addition of base (methoxide) to the internal ene-1,4-dione of the 4,5,6,7-tetrahydroindane nucleus. Yields of 2-phenyl-2-[2-(3-pyridyl)methyl]4,5,6,7-tetrahydroindan-1,3-dione **58** were not sufficiently high to attempt subsequent selective catalytic hydrogenation of the pyridine ring.

*Synthesis of 2-Substituted Indan-1,3-diones and 2-Substituted Tetrahydroindan-1,3-diones Containing 2-Substituted Quinoline, Tetrahydroquinoline, 2-(ω-*N*-Phthalimidoalkyl)-1,3-diones, and 5-Ethyl-Substituted Pyridyl Nuclei. Selective and Non-Selective Catalytic Hydrogenation of the Pyridine Ring Functionality*

We were further interested to investigate the generality of the ring cyclization–expansion sequence, as undergone by compound **2**, by variation of the heterocyclic component, in particular, by the introduction of a quinoline ring. This was achieved by a Michael-type addition of 2-vinylquinoline, prepared by the method of Kotan and Surnina,[21] to 2-phenyl-indan-1,3-dione (75%) (Scheme 3) to yield the quinoline adduct **15**. Selective catalytic hydrogenation of the pyridine ring was achieved at room temperature and pressure using Adam's platinium oxide as the catalyst, together with a trace of acid, to yield the selective 1,2,3,4-tetrahydroquinoline-reduced compound **16** in a 64% yield. Basification generated the free amine. However, unlike the corresponding piperidyl structure **2**, it failed to undergo the potential ring cyclization–expansion reaction to a nine-membered ring. We believe that this is due to two reasons: (1) a reduction in the nucleophilicity of the amine by conjugation of its lone pair with the fused benzene ring, and (2) the steric bulk associated

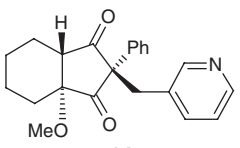


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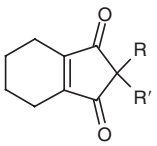
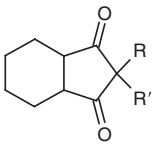
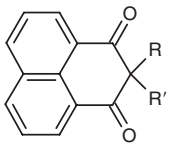
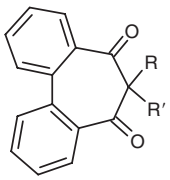
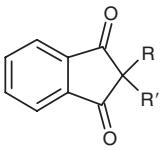
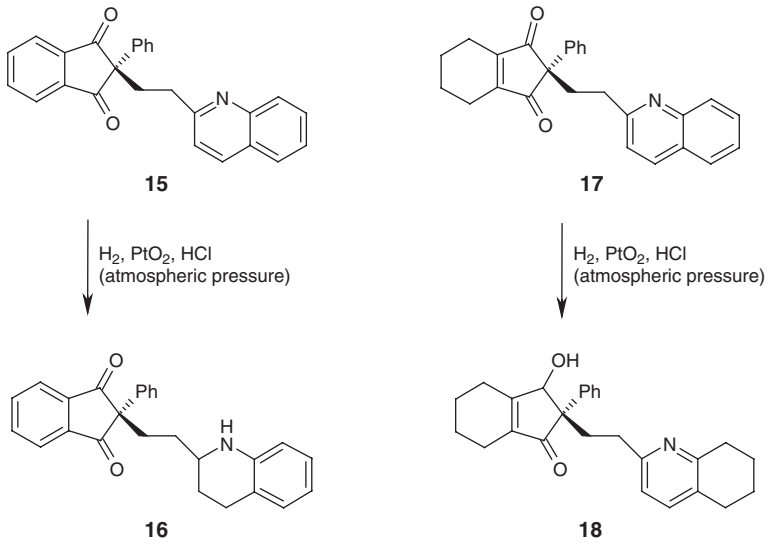
Fig. 3.

Table 1. 1,3-Dione-containing structures

Structure	Compound	R	R′
	**10**	Ph	2-(2-Piperidyl)ethyl
	9	Ph	2-(2-Pyridyl)ethyl
	11a/11b	Ph	2-(2-(*N*-Acetyl)piperidyl)ethyl
	58	Ph	2-(2-Pyridyl)methyl
	59	Ph	2-(2-Piperidyl)methyl
	60	Ph	2-(3-Pyridyl)methyl
	17	Ph	2-(2-Quinolyl)ethyl
	19	Ph	2-(2*N*-Ethylphthalimido)
	21	Ph	2-(3*N*-Propylphthalimido)
	**12**	Ph	2-(2-Pyridyl)ethyl
	13	Ph	2-(2-Piperidyl)ethyl
	**35**	Ph	2-(2-Pyridyl)ethyl
	36	Ph	2-(2-Piperidyl)ethyl
	**38**	Ph	2-(2-Pyridyl)ethyl
	39	Ph	2-(2-Piperidyl)ethyl
	**2**	Ph	2-(2-Pyridyl)ethyl
	24	Ph	2-(5-Ethyl-2-pyridyl)ethyl
	61	Me	2-(2-Pyridyl)ethyl
	62	Ph	2-(2-Pyridyl)methyl
	63	Ph	2-(2-Piperidyl)methyl
	15	Ph	2-(2-Quinolyl)ethyl
	16	Ph	2-(2-(1,2,3,4-Tetrahydroquinolyl)ethyl)
	29	Ph	2-(3*N*-Phthalimidopropyl)
	41	Me	2-(2*N*-Phthalimidoethyl)
	45	Me	2-(3*N*-Phthalimidopropyl)
	53	Me	2-(4*N*-Phthalimidobutyl)

with the benzo-fused ring system energetically disfavouring nucleophilic attack at the keto-groups.

In the light of the piperidyl-substituted tetrahydroindan-1,3-dione compound **1** possessing marked analgesic activity, we prepared additional variants of this compound. The new quinoline variant **17** was similarly synthesized (see above) by a Michael-type addition of 2-phenyl-4,5,6,7-tetrahydroindan-1,3-dione **7** to 2-vinylquinoline (63%) (Scheme 3) to yield the adduct **17**. Selective catalytic hydrogenation of the pyridine ring of the quinoline nucleus, over other present functionalities, could not be realized under identical hydrogenation conditions to those used for the unsaturated-indan **15**. The sole product isolated had surprisingly undergone reduction to the 5,6,7,8-tetrahydroquinoline, with concomitant reduction of one of the keto-groups to yield **18** (Schemes 4 and 5). This is an unusual result since it is known that in the presence of acid, both pyridine, and the pyridine portion of quinoline rings, can be selectively hydrogenated over other present functionalities, in particular, ketone groups. We believe that in the case of the fully unsaturated indan-containing system **15**, the mostly, overall, planar geometry of the molecule allows it to adhere, to a greater extent, planar to the surface of the catalyst, thus allowing the expected selective reduction of the pyridine nucleus to occur. However, in the case of the tetrahydroindan-containing variant **17**, the molecule is unable to adhere to the surface of the catalyst as effectively as the more planar unsaturated indan-nucleus **15** (see Fig. 4), due to the slight increase in steric bulk associated with the partially saturated nucleus (half chair conformation of the cyclohexene ring) and, more importantly, due to its resultant overall conformation. This possibly leads to the pyridine portion of the quinoline-ring system being unable to adhere to the catalyst surface as effectively as the benzene portion of the quinoline ring. The result of this very small change in overall hydrogenation geometry leads to the preferential and selective



Scheme 3. Selective and non-selective catalytic hydrogenations of the pyridine nuclei of fully unsaturated indan- and tetrahydroindan-1,3-diones.

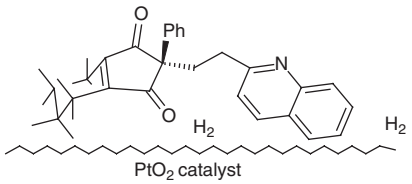


Fig. 4. Compound **17** is unable to adhere to the surface of the catalyst effectively due to the slight increase in steric bulk associated with the partially saturated nucleus (half chair conformation of the cyclohexene ring) and, more importantly, due to its resultant overall conformation.

hydrogenation of the benzene ring. (Note: for compound **24** (see below), the introduction of a 5-ethyl substituent onto the pyridine ring also alters the expected course of selective catalytic hydrogentation.)

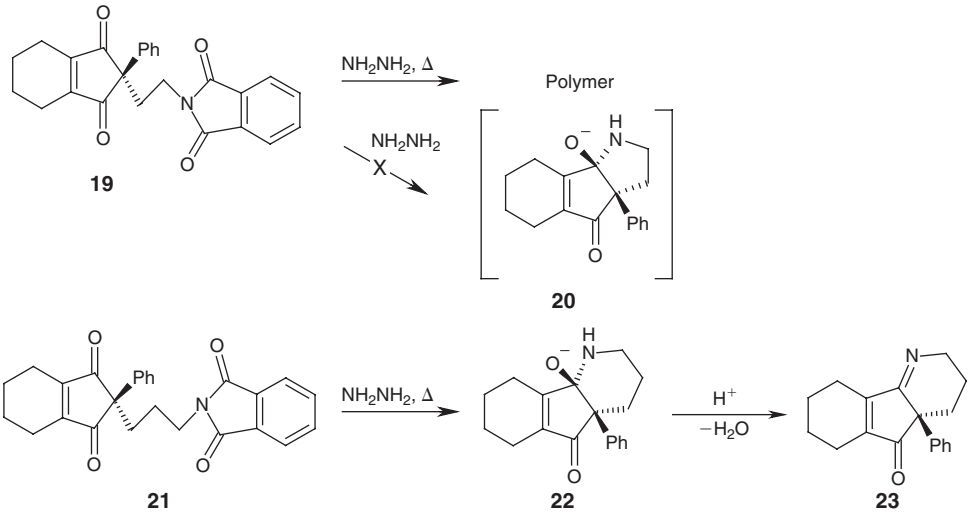
In the light of the novel ring cyclization–expansion reaction of **2**, we were further interested to investigate the applicability of this reaction to systems containing both tetrahydroindan-1,3-dione and 2-(ω-*N*-phthalimidoalkyl)-1,3-dione functionalities, i.e., **19** and **21** (Scheme 4). These compounds, on hydrazinolysis, produce primary aminoalkyl groups, as opposed to the secondary amine groups discussed thus far, and are, therefore, expected to behave and react differently.

Synthesis of the 2-(*N*-phthalimidoethyl) compound **19** was achieved via reaction of the sodio-derivative of 2-phenyl-4,5,6,7-tetrahydroindan-1,3-dione with *N*-(2-bromoethyl)phthalimide (38%) (see Accessory Materials).

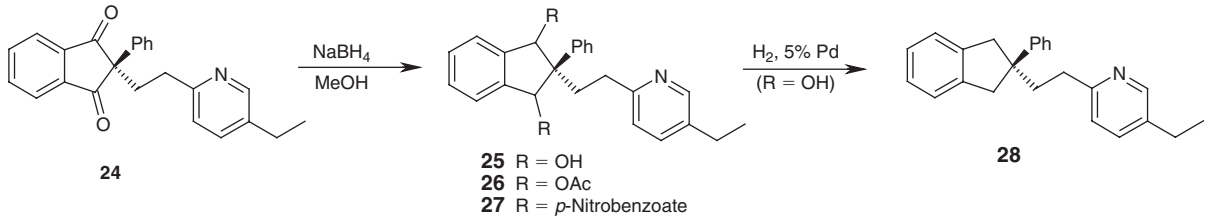
Hydrazinolysis of the 2-(*N*-phthalimidoethyl) compound **19** was performed in order to release the primary amine (de-protection), which was expected to subsequently undergo intra-molecular ring cyclization–expansion to yield an eight-membered ring, however the reaction mixture consisted of a polymer from which no characterizable products could be obtained. Retrospectively, this is perhaps not surprising since, in addition to generation of the required free primary amine, there exists the possibility of nucleophilic attack of the hydrazine across the activated ene-1,4-dione bond. In addition, there are further tandem possibilities for the generated primary amine to subsequently undergo intermolecular Michael-type additions across the activated ene-1,4-dione functionality. However, it is interesting to note that the synthesis of the structurally related 3-(*N*-phthalimidopropyl) derivative **21** (see the Experimental), followed by hydrazinolyis, yielded the new ring structure **23**, via direct ring cyclization and condensation, in a surprisingly good 40% yield. In this instance it is considered that initial formation of the six-membered carbinolamine-containing intermediate **22** is energetically far more favourable (hence the 40% yield) than the possible five-membered carbinolamine-containing intermediate **20**, the latter system thus favouring polymerization reactions over ring cyclization.

We previously mentioned that the preparation of the tetrahydro-quinoline substituted system **15**, followed by selective catalytic hydrogenation of the pyridine nucleus, to undergo the ring cyclization–expansion reaction (in comparison with **3**) failed, principally for two reasons. In continuing to investigate the limitation of the structural parameters required to affect the ring-expansion transformation we decided to make further attempts at modifying the 2-pyridyl grouping so as to minimize these issues. It was envisaged that this could be achieved by the placement of a small alkyl group on the pyridine ring, in this case a 5-ethyl substituent. This substitution would both reduce the steric effects, present in the potential carbinolamine intermediate, and, by 'remote' placement (5-substitution) of a small alkyl group, minimize interference of nucleophilic attack of the nitrogen lone-pair at the keto-groups.

The above predictions were investigated via synthesis of the 5-ethyl-pyridyl analogue **24** (Scheme 5), via a Michael-type addition between 2-vinyl-5-ethyl pyridine and 2-phenyl-indan-1,3-dione, however, no selective catalytic hydrogenation of the 5-ethyl-substituted pyridine ring could be obtained over other present functionality, i.e. the



Scheme 4.



Scheme 5.

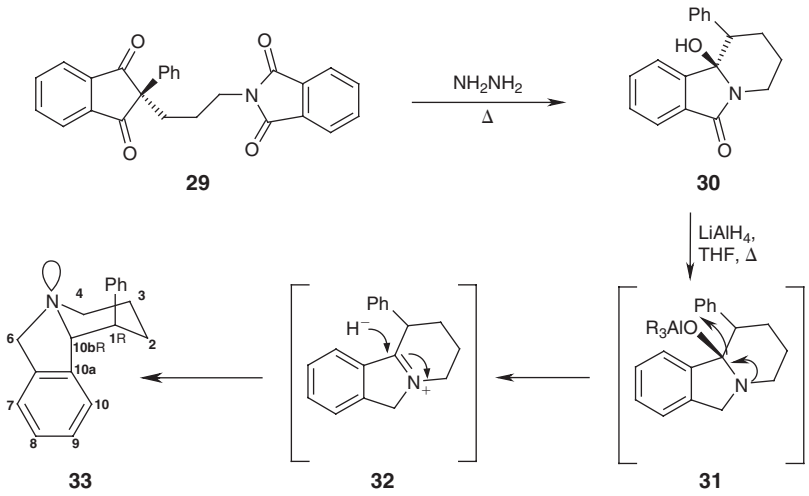
ketone groups. We believe the unexpected non-selective hydrogenation of the pyridine ring arises from the increase in steric bulk associated with alkyl-substitution, which disfavours adhesion to the catalyst surface. Based on the above results, and the fact that other appropriately substituted 2-vinyl pyridine analogues were not readily accessible, no attempts to synthesize further derivatives were made. (Some attempts were made at synthesizing α- and β-methyl-substituted 2-vinyl pyridine analogues; however, the yields were low and thus did not lend themselves to a large-scale synthesis required in order to further investigate the ring-expansion transformation.)

With the aim to produce some further new indan-1,3-dione structures, compound **24** was reduced using sodium borohydride to yield a mixture of the *cis*- and *trans*-alcohols **25** which could not be separated using chromatography. Derivatization of the diol as its di-acetate **26** or di-*p*-nitrobenzoate **27** allowed partial isomer separation. Hydrogenolysis of the diol over 5% Pd/C cleanly gave the new indan system **28** in good yield.

The structural variations made thus far have primarily centred on modifications to the indan- and 2-pyridylalkyl-groupings. We were further interested to test the generality and applicability of the novel ring expansion reaction to systems possessing a 2-alkyl substituent on the indan structure, as opposed to the 2-phenyl of the parent molecule.

This was achieved by the initial synthesis of 2-methylindan-1,3-dione,[22] and subsequent Michael-type addition to 2-vinylpyridine, to yield the new indan-1,3-dione **61** (see Accessory Materials). Selective catalytic hydrogenation of the pyridine ring, over other present functionalities, could not be achieved (the resulting mixture produced a polymeric material and column chromatography yielded no characterizable products). The authors attribute this instability to the 2-methyl-1,3-dione functionality, and its containment within a strained five-membered ring.

Further structural modifications, in order to ascertain the necessary functional groups and structural paramenters for the ring cyclization–expansion to occur, were made. In particular, we were interested in determining whether a shortening of the 2-ethyl linking group to a 2-methyl group, for the fully unsaturated indan-1,3-dione, would still allow the ring cyclization–expansion reaction to progress. This was achieved via the initial synthesis of 2-picolyl chloride hydrochloride, mentioned previously, and alkylation of this molecule with the sodio-derivative of 2-phenyl-indan-1,3-dione in the presence of two equivalents of base to yield **62** (see Accessory Materials). Selective catalytic hydrogenation of the pyridine ring yielded the piperidyl compound **63**, however, no products corresponding to a possible ring cyclization–expansion reaction, as for the 2-ethyl-piperidyl compound **3**, were identified. We believe this is due to the piperidyl group not being able to adopt the conformation required to allow nucleophilic attack of the nitrogen lone pair at the carbonyl groups, and simultaneously, it not being able to form the required, strained, and energetically unfavourable



Scheme 6.

five-membered-ring carbinolamine-intermediate necessary for ring cyclization and subsequent expansion.

Synthesis of the New Bridged Ring System rel-*(1*R*,10b*R*)-1,2,3,4,6-Hexahydro-1-phenylpyrido[2,1-*a*]isoindole **33** by Selective Hydride Reduction of 1,2,3,10b-Hydroxy-1-phenylpyrido[2,1-*a*]isoindol-6(4H)-one **30***

Pyridine, quinoline, and their selectively reduced secondary amine containing structures have been extensively explored, as described throughout this paper. Also of interest, particularly in ascertaining their ability to undergo the ring cyclization–expansion reaction sequence, are primary amine containing structures.

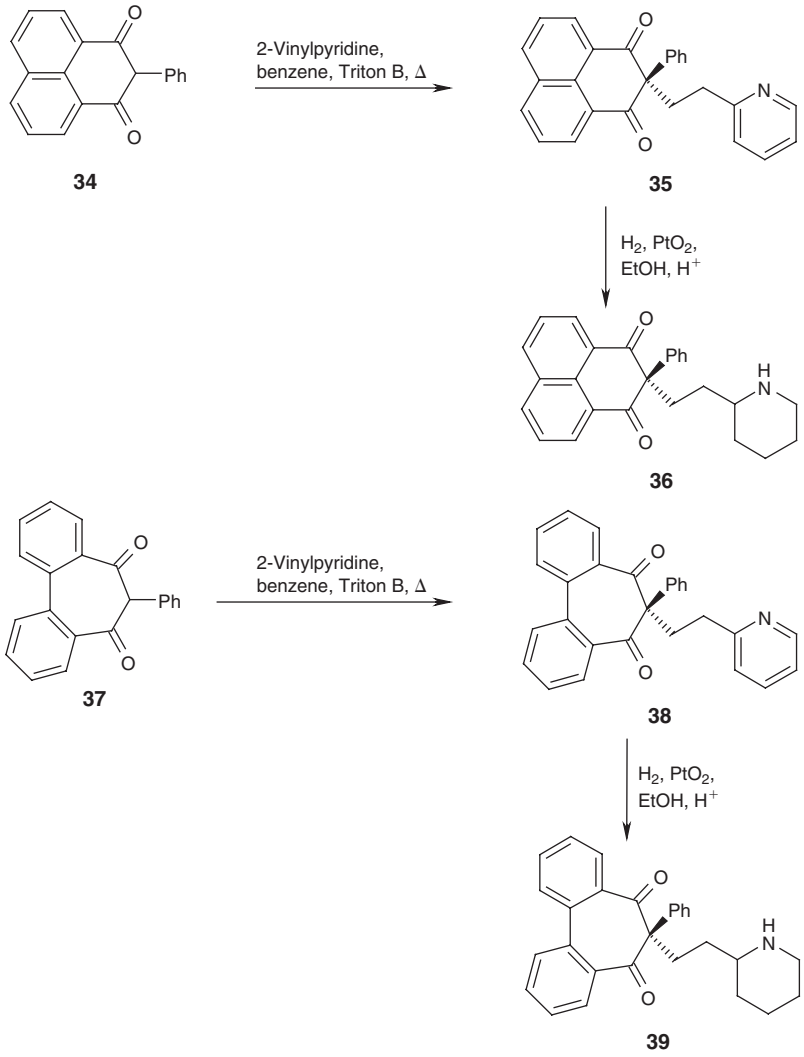
The synthesis of 2-phenyl-2-(3-*N*-phthalimidopropyl)-indan-1,3-dione **29** has been reported, and its hydrazinolysis yielded 1,2,3,4,6-tetrahydro-10b-hydroxy-1-phenylpyrido-[2,1-*a*]isoindol-6(4H)-one **30** as the major product (Scheme 6).[23]

In an attempt to produce some further new and unexplored nitrogen-containing heterocycles, we attempted a lithium aluminium hydride reduction of this compound, which produced a surprising result (Scheme 6). It is postulated that reduction of the tertiary amide occurs with concomitant coordination of the alcohol group to the aluminium to give the intermediate **31**. Displacement of the aluminium-coordinated alcohol by anchimeric assistance from the tertiary amine probably yields the iminium ion **32**, which is further reduced by the hydride to yield the new 1,2,3,4,6-hexahydro-1-phenylpyrido[2,1-*a*]-isoindole **33**. The IR spectrum of **33** showed no Bohlman bands (found in systems containing *trans*-ring fusions) thus indicating a *cis*-ring fusion. The C(10b) bridgehead proton in the ^{1}H NMR spectrum at δ 3.8 appeared as a slightly broadened singlet, which indicated a torsional angle of approx. 60° between the C(1)-H and C(10b)-H bonds. The phenyl substituent was thus assigned the *axial* orientation. Further evidence for the *axial* phenyl group is the magnitude of couplings between the C(1) and C(2) protons, of 5 Hz, consistent with bisection of the C(2) methylene by the C(1)-H bond. The C4H$_{ax}$ and C4H$_{eq}$ protons appear at δ 2.57 (J_{gem} −12, $J_{4,3}$ 12) and δ 3.2 (J_{gem} −12), which supports a chair conformation for the piperidine ring. The stereochemistry is thus depicted as shown in **33** and is assigned as *rel*-(1*R*, 10b*R*)-1,2,3,4,6-hexahydro-1-phenylpyrido[2,1-*a*]isoindole.

Synthesis of 2-Phenyl-2-[2-(2-pyridyl)ethyl]-Substituted 1,3-Diones Possessing Six- and Seven-Membered Ring-Containing 1,3-Dione Units

In the light of the novel route to medium-ring nitrogen-containing heterocycles, afforded by catalytic hydrogenation of the pyridine ring of **2**, we decided to explore the applicability of this reaction to analogous systems possessing the 1,3-dione functionality within both six- and seven-membered rings, in the hope of obtaining, by a similar transformation, ten- and eleven-membered rings.

Modification of the size of the ring containing the 1,3-dione functionality **35**, **36**, **38**, and **39** (Scheme 7) was achieved by the initial syntheses of the six-membered **34**[24–26] and seven-membered **37**[27] 1,3-dione-containing units. Michael-type addition of 2-vinylpyridine to these nuclei under aprotic conditions, in a seven day benzene reflux, using Triton B as the catalyst gave the new pyridine adducts **35** and **38**, respectively. Selective catalytic hydrogenation of the pyridine rings in ethanol solvent over platinum oxide catalyst, containing hydrochloric acid, gave the piperidyl variants **36** and **39**, respectively, after basification. Both systems were isolated and stable as their free bases. It is interesting to note that unlike the five-membered 1,3-dione-containing ring system, both the six- and seven-membered 1,3-dione-containing rings did not undergo the potential ring cyclization–expansion transformation to ten- and eleven-membered nitrogen heterocycles. The authors believe that the failure of the above two systems to undergo the ring cyclization–expansion transformation are almost entirely related to the relief of ring strain on ring-expansion. (The fully unsaturated indan-1,3-dione, possessing a five-membered 1,3-dione-containing ring is considerably more strained in both the six- and seven-membered 1,3-dione-containing rings.) These two results proved useful during this



Scheme 7.

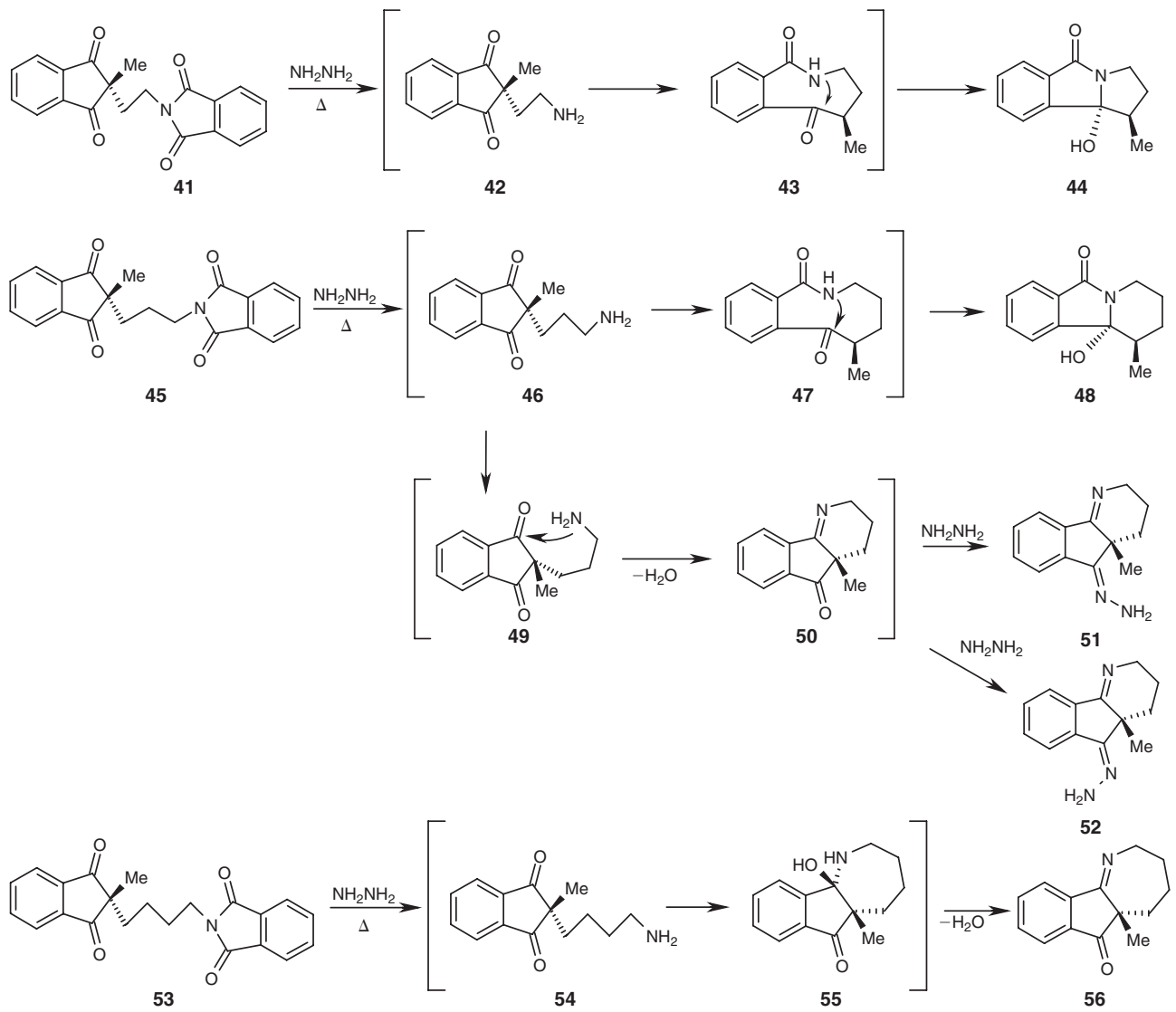
synthetic program in dictating the structure and functionality that is needed in the design of further possible chemical entities that may potentially undergo the novel ring-expansion reaction.

*Ring Cyclization–Expansion–Transannular Contraction, and Cyclization Reactions of Hydrazinolyzed 2-Methyl-2-(ω-*N*-phthalimidoalkyl)indan-1,3-diones*

In continuing to investigate and explore the generality of the novel ring cyclization–expansion reaction found to occur for structure **3** (Scheme 1), we decided to replace both the 2-aryl substituent with a 2-alkyl group, and, simultaneously, the 2-ethyl-piperidyl group with various ω-(*N*-phthalimidoalkyl) groups (Scheme 8). This would further enable us to identify the applicability and scope of this reaction to indan-1,3-diones possessing both 2-alkyl and ω-(*N*-phthalimidoalkyl) groups to potentially lead to the generation of several new medium-ring alkyl-substituted nitrogen-containing heterocycles. In addition, the structures and reactions of these particular compounds had not previously been explored.

In particular, we were interested in applying this reaction to the three new 2-methyl-2-(ω-(*N*-phthalimidoalkyl))indan-1,3-dione structures, and specifically those containing 2-(*N*-phthalimidoethyl) **41**, 3-(*N*-phthalimidopropyl) **45**, and 4-(*N*-phthalimidobutyl) **53** groups, which possess the potential to generate eight-, nine-, and ten-membered nitrogen-containing heterocycles by the aforementioned reaction sequence.

Initial syntheses of the new 2-methyl-2-(ω-(*N*-phthalimidoalkyl))indan-1,3-diones were achieved using the method previously and successfully adopted for the syntheses of 2-phenyl-2-(ω-(*N*-phthalimidoalkyl))indan-1,3-diones,[28] however, the yields were much lower and were accompanied by significant quantities of side products. This is exemplified for the synthesis of 2-methyl-2-(3*N*-phthalimidopropyl)indan-1,3-dione **45**, which produced, in addition to the required *C*-alkylated product **45** (14%), the side product (40%) **40** (Fig. 5) which was isolated and identified as the *O*-alkylated compound. This is a contrasting result to that obtained when the analogous alkylation reactions, i.e., the generated carbanion of 2-phenyl-indan-1,3-dione was reacted with the corresponding



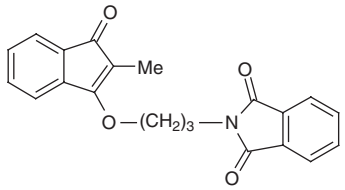
Scheme 8.

2-(*N*-phthalimidoalkyl)bromo compounds (alkyl = ethyl, propyl, butyl), were performed. In this latter instance we believe the generated carbanions possess their charge localized and stabilized on C-2 by the 2-phenyl group, which results predominantly in *C*-alkylation. However, in the case of the 2-methyl substituted indan-1,3-diones, a destabilization of the generated carbanion occurs (via an inductive effect from the 2-methyl group), which results in an equilibrium situation favouring predominant formation of the enolate structure (Scheme 9) and thus preferential *O*-alkylation.

Synthesis of **44** was achieved via hydrazinolysis of **41** to yield the new heterocyclic system **44** (25%). The intermediate primary amino structures **42**/**43** were not isolated, forming, in situ, the ring structure **44**. This is postulated to occur by initial nucleophilic attack of the amine on one of the keto-groups, to yield an intermediate cyclic-carbinolamine (compare with **4**, Scheme 1). Further rearrangement, by ring-expansion, of this carbinolamine produces the eight-membered ring intermediate **43**, which subsequently, by transannular-cyclization, yields the new tricyclic system **44**. (This eight-membered ring-containing intermediate **43**, unlike **5**, possesses a secondary amide functionality, which allows further transannular reaction to produce the 5,5-ring-contracted amide structure **49** to occur.)

Hydrazinolysis of the 3-(*N*-phthalimidopropyl) derivative **45** yielded **48** via a similar cyclization–expansion-transannular reaction, however, in addition, the two hydrazone products **51** and **52** were produced. In this instance it is possible that the six-membered carbinolamine-containing ring intermediate (compare with **4**) is energetically more stable than that of the five-membered ring-intermediate produced upon the hydrazinolysis of **41**. This intermediate, therefore, probably does not have to so readily (or possibly more slowly) undergo ring expansion to relieve this strain, i.e., formation of a 5,6-ring-fused system, as opposed to a 5,5-ring-fused system: This facilitates dehydration of the carbinolamine intermediate to the imine **50**. Subsequent reaction of the keto group with hydrazine yields the two isomeric hydrazones **51** and **52**.

The transition of reaction products throughout this sequence of compounds is further exemplified by hydrazinolysis of the 4-(*N*-phthalimidobutyl) compound **53**, which



40

Fig. 5.

yields the azepine-containing structure **56** as the sole product. In this instance it is interpreted that the seven-membered carbinolamine intermediate **55** does not energetically favour/require ring expansion, but simply undergoes ring cyclization followed by condensation.

Overall, in transcending this series of homologous ω-(*N*-phthalimidoalkyl)-substituted indan-1,3-diones there is a very subtle, but complex, interplay between steric, thermodynamic, and electronic factors. This combination of factors dictates the outcome of these reactions by influencing both the nature of products and their relative amounts.

*Hydride-Induced Transannular–Contraction Reaction of the Nine-Membered Ring-Containing Nitrogen Heterocycle **6** (Lactam-to-Lactone Interchange)*

Lastly, in continuing to investigate the chemistry of some of the final ring structures we turned our attention to the nine-membered ring-containing structure **6**,[11,29] whose modified structures, and resultant stereochemistries have been studied.[19,30] Further attempts to modify the structure of this medium-sized ring, and explore its reactivity and behaviour, led us to investigate a sodium borohydride reduction (Scheme 10) with the expectation of realizing selective reduction of the keto-group. This was initially achieved, however, the resulting alcohol was surprisingly found to undergo a lactam-to-lactone transannular atom interchange to yield the novel ring-contracted lactone-containing system **57**.

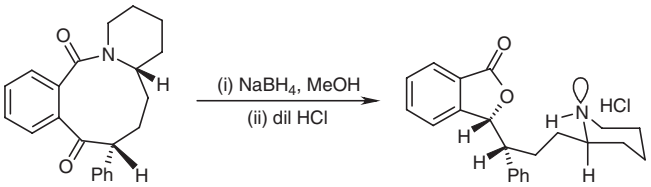
Pharmacological Test Results of Analgesic Screening of Selected Compounds

The hydrochloride of 2-phenyl-2-[2-(2-piperidyl)ethyl]-4,5,6,7-tetrahydroindan-1,3-dione **1** possesses marked analgesic activity (100% inhibition referenced to codeine).[10] The previously unreported pharmacological test results of ten selected compounds, for analgesic activity, are detailed in Table 2, of which six compounds possess between 58% and 8% inhibition, with a further two exhibiting moderate and 'some' activity. (Note: we have/had no control over the decision of which compounds were pharmacologically tested, or over the limited results with which we were furnished.)

Conclusions

We have described the synthesis of thirty-eight new nitrogen-containing heterocyles, which are related in structure to many current classes of known drugs. These structures possess the potential to be biologically active and may, therefore, be of benefit to medicinal chemists working in these areas, and who

Scheme 9.



Scheme 10.

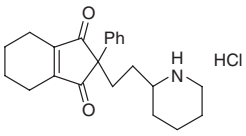
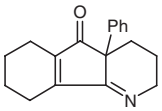
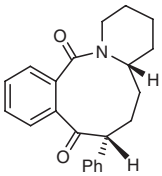
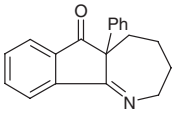
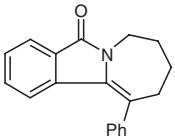
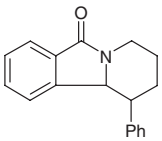
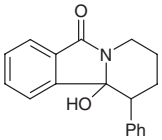
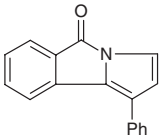
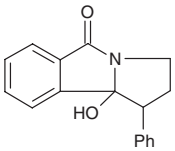
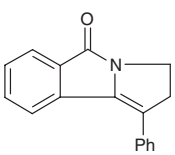
may wish to further explore these compounds as potential drug candidates. Specifically, we reported the synthesis of **1** which possessed marked analgesic activity (100% inhibition referenced to codeine) and a further five compounds exhibiting moderate activity to several pharmacological tests.

In addition, we have thoroughly explored and investigated the applicability and generality of the novel ring cyclization–expansion reaction of 2-phenyl-2-[2-(2-piperidyl)ethyl]indan-1,3-dione **3**, described in Scheme 1, to systems containing a variety of functionalities. We conclude that in order for the ring cyclization–expansion reaction sequence to occur, a fully unsaturated indan-1,3-dione group needs to be present. A 2-phenyl group is not a requirement as ring-expansion occurs for the 2-methyl substituted compounds **42** and **46**. Furthermore, a 2-(piperidyl)ethyl group is also not a necessity as ring expansion was found to occur with both 2-*N*- and 3-*N*-phthalimidopropyl groups, however, in these latter two cases, the intermediates possessing secondary amide functionality undergo subsequent ring-contraction reactions to form the new nitrogen-containing heterocycles **44**, **48**, **51**, and **52**. A limitation of this ring-expansion reaction, related to the length of the ω-*N*-phthalimidoalkyl group, is noted, i.e., the 4-*N*-phthalimidobutyl-substituted compound **53** undergoes simple ring cyclization to form the new azepine-containing heterocycle **56** (azepine-containing structures are also of medicinal interest since they also possess many of the biological properties mentioned above for medium-sized rings).[14–16]

In spite of the fact that structures containing the 1,2,3,4-tetrahydroindan-1,3-dione nuclei failed to undergo the ring-expansion reaction sequence, they were not totally without reactivity since the 2-phenyl substituted compound **21** underwent direct cyclization to form the new heterocyclic system **23**.

Overall, we have defined many of the functional group parameters necessary for the novel ring cyclization–expansion reaction sequence to occur. This will be of use to chemists who may wish to consider and utilize this useful ring-expansion reaction as part of a wider synthesis, or to synthesize other medium-sized rings.

Table 2. Pharmacological test results of analgesic screening of selected compounds
All compounds administered orally.

Compound	Ref.	Test (Mice)	Dose [mg kg^{-1}]	Result[A]	Remarks[B]
		Acetylcholine induced writhing	100	++	100% inhibition
		Hot plate	100	−	Inactive
		Inflamed paw pressure	75	++	Marked activity
		Normal paw pressure	75	±	Negligible activity
		Antipyretic activity	75	−	Inactive
		Acetylcholine induced writhing	100	±	42% inhibition
		Hot plate	100	−	
	[2]	Acetylcholine induced writhing	100	−	0% inhibition
		Hot plate	100	−	
	[23]	Acetylcholine induced writhing	100	±	25% inhibition
		Hot plate	100	−	
	[23]	Acetylcholine induced writhing	100	−	8% inhibition
		Hot plate	100	−	
	[23]	Acetylcholine induced writhing	100	++	58% inhibition
		Hot plate	100	−	Moderate activity
	[23]	Acetylcholine induced writhing	100	−	17% inhibition
		Hot plate	100	−	
	[28]	Acetylcholine induced writhing	100	−	0% inhibition
		Hot plate	100	−	
	[28]	Acetylcholine induced writhing	100	−	0% inhibition
		Hot plate	100	−	
	[28]	Acetylcholine induced writhing	100	±	25% inhibition
		Hot plate	100	+	Some activity

[A] ++ Marked activity, + moderate activity, ± negligible activity, − inactive.
[B] Reference drug codeine.

Lastly, several interesting new compounds and selective functional group interconversions have been uncovered during the course of this programme, these include: the reductive formation of the new bridged nitrogen-containing heterocyclic system **33**, the transannular-contraction reaction of **6** to form the new lactone-containing system **57**, and finally, the selective catalytic hydrogenation, under identical physical conditions, of the pyridine and benzene rings of the quinoline-substituted systems **15** and **17**.

Experimental

Elemental analyses were carried out at Glaxo Group Research Limited. ^{1}H NMR spectra were determined at 60 MHz with a Varian T60 spectrometer and for 270 MHz with a Bruker Spectrospin WH-270 FT NMR spectrometer. ^{13}C NMR spectra were determined with a JEOL GSX 270 FT NMR spectrometer. Mass spectra were recorded on a JEOL JMS-DX303 GC/mass spectrometer. Column chromatography was carried out over silica. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected.

2-Phenyl-2-[2-(2-piperidyl)ethyl]-4,5,6,7-tetrahydroindan-1,3-dione ***10***

A solution of 2-phenyl-2-[2-(2-pyridyl)ethyl]4,5,6,7-tetrahydroindan-1,3-dione **9** (4 g, 12 mmol) in methanol (100 mL) and concentrated hydrochloric acid (1.5 mL) were hydrogenated at atmospheric pressure and room temperature in the presence of PtO_2 (0.3 g) until the calculated amount of hydrogen had been taken up. The catalyst was filtered off and the solvent reduced in volume. Recrystallization of the yellow solid, which separated on standing, from ethanol gave *2-phenyl-2-[2-(2-piperidyl)ethyl]-4,5,6,7-tetrahydroindan-1,3-dione hydrochloride* **10** as a pale yellow crystalline solid (4.1 g, 91%), mp 240°C. (Found: C 70.5, H 7.5, N 3.7%. $C_{22}H_{28}NO_2Cl$ requires C 70.6, H 7.5, N 3.7%.) ν_{max}($CHCl_3$)/cm^{-1} 1740, 1700, 1660, 1600. δ_H ($CDCl_3$) 8.5–8.7 (5H, m, aromatic), 1.1–2.2 (18H, m, aliphatic).

N-*Acetyl-2-phenyl-2-[2-(2-piperidyl)ethyl]-4,5,6,7-tetrahydroindan-1,3-dione* ***11a/11b***

2-Phenyl-2-[2-(2-piperidyl)ethyl]-4,5,6,7-tetrahydroindan-1,3-dione **10** (0.5 g, 1.5 mmol) was dissolved in a 1 : 1 mixture of dried triethylamine and pyridine (20 mL) and the mixture was cooled to 0°C. Acetylchloride (0.6 g, 15 mmol) was slowly added and the mixture was allowed to stand for 24 h at room temperature. After this period, the mixture was extracted with ether and the combined extracts were dried (Na_2SO_4). The ether was removed under reduced pressure to give an oil. Chromatography of the oil over silica using ether/petroleum ether (20/80) as the elutant gave N-*acetyl-2-phenyl-2-[2-(2-piperidyl)ethyl]-4,5,6,7-tetrahydroindan-1,3-dione* **11a/11b** as a yellow oil (0.31 g, 55%). (Found: C 76.0, H 7.7, N 3.6%. $C_{24}H_{29}NO_3$ requires C 75.9, H 7.7, N 3.7%). ν_{max} ($CHCl_3$)/cm^{-1} 1730, 1685, 1630, 1600. δ_H ($CDCl_3$) 4.7 (1H, m, PhCCH), 4.5 (1H, dd, $PhCCH_2CH$), 3.7 (1H, m, $NCH(CH_2)_2$), 3.5 (1H, br d, NCH_{eq}), 3.0 (1H, br t, NCH_{ax}), 2.1 (3H, s, CH_3), 2.06 (3H, s, CH_3). *m/z* 379 (M^+), 336 ($M^+ - CH_3CO$), 154 ($M^+ - CH_2CH_2CH(CH_2)_4NCOCH_3$), 91 ($PhCH_2$), 77 (Ph), 43 ($CH_3O$).

Hexahydro-2-phenyl-2-[2-(2-pyridyl)ethyl]-indan-1,3-dione ***12***

Zinc dust (5 g) was added to a solution of 2-phenyl-2-[2-(2-pyridyl)ethyl]4,5,6,7-tetrahydroindan-1,3-dione **9** (2.6 g, 7.9 mmol) in glacial acetic acid (400 mL) and the mixture heated in a boiling water bath for 25 min. The zinc was filtered off and the solvent was removed under reduced pressure. Saturated sodium bicarbonate solution was added and the mixture was extracted with chloroform. The combined extracts were dried (Na_2SO_4) and the solvent was removed under reduced pressure to give a thick oil. Crystallization occurred from ether/ethanol, 50/50, to give a white solid. Several recrystallizations from ether/ethanol gave *hexahydro-2-phenyl-2-[2-(2-pyridyl)ethyl]-indan-1,3-dione* **12** as white plates (1.88 g, 60%), mp 116–117°C. (Found: C 79.3, H 6.9, N 4.2%. $C_{22}H_{23}NO_2Cl$ requires C 79.3, H 7.0, N 4.2%.) ν_{max} (Nujol)/cm^{-1} 1755, 1730, 1600, 750. δ_H ($CDCl_3$) 7.3 (9H, ArH), 3.0 (2H, m, $(COCH)_2$), 2.3–2.8 (4H, m, $(COCHCH_2)_2$), 1.7 (4H, m, $(COCHCH_2CH_2)_2$).

Hexahydro-2-phenyl-2-[2-(2-piperidyl)ethyl]-indan-1,3-dione Hydrochloride ***13***

Hexahydro-2-phenyl-2-[2-(2-pyridyl)ethyl]4,5,6,7-tetrahydroindan-1,3-dione **12** (0.5 g, 1.5 mmol) was dissolved in methanol and concentrated hydrochloric acid (0.2 g). PtO_2 catalyst (0.15 g) was added and the mixture was hydrogenated at atmospheric pressure and room temperature until the calculated amount of hydrogen had been taken up. The catalyst was filtered off and the methanol was reduced in volume. On allowing the solution to stand, a white crystalline solid was deposited. Recrystallization of this from methanol gave *hexahydro-2-phenyl-2-[2-(2-piperidyl)ethyl]-indan-1,3-dione hydrochloride* **13** as a white powder (0.32 g, 56%), mp 177–179°C. (Found: C 67.8, H 7.8, N 3.6%. $C_{22}H_{30}NO_2Cl{\cdot}0.75H_2O$ requires C 67.8, H 7.7, N 3.6%.) ν_{max} (Nujol)/cm^{-1} 3500, 1740, 1710, 1600, 750. δ_H ($CDCl_3$) 9.5 (2H, s, NH_2), 7.3 (5H, m, ArH), 3.5 (1H, m, $(Ph)CCH_2CH_2CHN$).

2-Phenyl-2-[2-(2-piperidyl)methyl]-4,5,6,7-tetrahydroindan-1,3-dione Hydrochloride ***59***

2-Phenyl-2-[2-(2-pyridyl)methyl]4,5,6,7-tetrahydroindan-1,3-dione **58** (4 g, 13 mmol) was dissolved in methanol and concentrated hydrochloric acid (0.5 mL). PtO_2 Catalyst (0.15 g) was added and the mixture was hydrogenated on a Parr Hydrogenator until the calculated pressure change had occurred. The catalyst was filtered off and the solvent was removed under reduced pressure to give an off-yellow oil. On standing at low temperature for one week in absolute ethanol, a yellow crystalline solid was formed. Several recrystallizations from ethyl acetate/methanol gave *2-phenyl-2-[2-(2-piperidyl)methyl]-4,5,6,7-tetrahydroindan-1,3-dione hydrochloride* **59** (0.7 g, 16%), mp 178–180°C. (Found: C 68.4, H 7.2, N 3.7%. $C_{21}H_{26}NO_2Cl{\cdot}0.5H_2O$ requires C 68.4, H 7.1, N 3.7%.) ν_{max} (Nujol)/cm^{-1} 3400, 1760, 1710, 1625, 1600, 750. δ_H ($CDCl_3$) 9.6 (1H, s, N^+H_a), 8.1 (1H, s, N^+H_b), 7.3 (5H, s, ArH), 3.5 (1H, d, N^+CH_{eq}), 2.9 (1H, m, $N^+CH(CH_2)_2$), 2.8 (1H, m, $N^+CH_{ax}CH_2$).

2-Phenyl-2-(2-[2-(1,2,3,4-tetrahydroquinolin-yl)]ethyl)indan-1,3-dione ***16***

2-Phenyl-2-(2-quinolylethyl)indan-1,3-dione **15** (11.7 g, 31 mmol) was dissolved in methanol and concentrated hydrochloric acid (3.7 mL). PtO_2 catalyst (0.7 g) was added and the mixture hydrogenated at atmospheric pressure and room temperature until the calculated amount of hydrogen had been taken up. The catalyst was filtered off and the solvent was removed under reduced pressure to give a thick dark oil. The residue was treated with aqueous sodium bicarbonate solution and extracted with chloroform. Passage of the organics over silica gave *2-phenyl-2-(2-[2-(1,2,3,4-tetrahydroquinolin-yl)]ethyl)indan-1,3-dione* **16** as a slightly yellow oil (7.6 g, 64%), R_f (chloroform) 0.54. (Found: C 82.2, H 6.2, N 3.5%. $C_{26}H_{23}NO_2$ requires C 81.9, H 6.0, N 3.7%.) ν_{max} (liquid film)/cm^{-1} 3400, 1735, 1700, 1600, 750. δ_H ($CDCl_3$) 6.8–7.8 (15H, ArH), 3.72 (1H, s, NH), 3.2 (1H, m, NCH_{eq}), 2.74 (2H, m, $ArCH_2$), 2.4 (2H, m, $C(Ph)CH_2$), 1.95 (1H, m, $ArCH_2CH_{eq}$), 1.66 (1H, m, $ArCH_2CH_{ax}$), 1.42 (2H, m, $C(Ph)CH_2CH_2$). *m/z* 381 (M^+).

2-Phenyl-2-[2-(2-quinolyl)ethyl]-4,5,6,7-tetrahydroindan-1,3-dione ***17***

2-Phenyl-4,5,6,7-tetrahydroindan-1,3-dione (10 g, 44 mmol) was heated under reflux for 40 h with 2-vinylquinoline (8.5 g, 55 mmol) in absolute ethanol (250 mL). The solution was concentrated to give an orange/yellow oil that was left to stand overnight whereupon a bright yellow crystalline solid formed. Recrystallization from absolute

ethanol gave *2-phenyl-2-[2-(2-quinolyl)ethyl]-4,5,6,7-tetrahydroindan-1,3-dione* **17** as a yellow crystalline sold (10.6 g, 63%), mp 111–112°C. (Found: C 76, H 6.6, N 3.9%. $C_{22}H_{23}NO_3$ requires C 75.8, H 6.59, N 4.0%.) ν_{max} (Nujol)/cm^{-1} 1730, 1680, 1630, 1600. δ_H ($CDCl_3$) 1.8 (4H, m, ($COCCH_2CH_2)_2$), 2.4 (4H, m, ($COCH_2)_2$), 2.6–3.0 (4H, m, CH_2CH_2). *m/z* 379 (M^+).

3-Hydroxy-2-phenyl-2-[2-(2,5,6,7,8-tetrahydroquinolyl)ethyl]-4,5,6,7-tetrahydroindan-1-one Hydrochloride ***18***

2-Phenyl-2-[2-(2-quinolyl)ethyl]-4,5,6,7-tetrahydroindan-1,3-dione **17** (6 g, 16 mmol) was dissolved in methanol and concentrated hydrochloric acid (5 mL). PtO_2 (0.5 g) was added and the mixture was hydrogenated on a Parr Hydrogenator until the calculated pressure change had occurred. The catalyst was filtered off and the solvent was removed under reduced pressure. On standing in ethanol overnight a white crystalline solid was formed. Recrystallization from methanol/ethyl acetate gave *3-hydroxy-2-phenyl-2-[2-(2,5,6,7,8-tetrahydroquinolyl)ethyl]-4,5,6,7-tetrahydroindan-1-one hydrochloride* **18** as a white crystalline solid (1.7 g, 26%), mp 176–178°C. (Found: C 72.0, H 7.2, N 3.2%. $C_{26}H_{28}NO_2Cl{\cdot}0.5H_2O$ requires C 72.1, H 6.9, N 3.2%.) ν_{max} (Nujol)/cm^{-1} 3500, 3300, 1700, 1625, 1600. δ_H ($CDCl_3$) 16.5 (1H, s, OH), 7.1–7.9 (9H, ArH), 6.8 (1H, s, CHOH).

*2,3,4,4a,6,7,8,9-Octahydro-4a-phenylindeno-[1,2-*b*]pyridine-5-one* ***23***

2-Phenyl-2-(3-phthalimidopropyl)-4,5,6,7-tetrahydroindan-1,3-dione **21** (8.1 g) was stirred and heated under reflux with hydrazine hydrate (1 mL) in ethanol (200 mL) for 1.5 h. The phthalhydrazide formed was filtered off and the filtrate was evaporated to dryness to give a yellow oil (3 g). The oil was chromatographed over silica using diethyl ether as the elutant to give to give *2,3,4,4a,6,7,8,9-octahydro-4a-phenylindeno[1,2-*b*]pyridine-5-one* **23** as a white crystalline solid (2 g, 40%), mp 129–130°C. (Found: C 81.8, H 7.2, N 5.2%. $C_{18}H_{19}NO$ requires C 81.5, H 7.2, N 5.2%.) ν_{max} ($CHBr_3$)/cm^{-1} 1700, 1650. λ_{max} (EtOH)/nm 261. δ_H ($CDCl_3$) 7.1–7.4 (5H, m, ArH), 3.75 (2H, m, $CH_2CH_2N(CH_2)_2$), 2.0–2.8 (5H, m, C-6H, C-9H, C-4H$_{eq}$), 1.4–1.6 (7H, m, C-3H, C-4H$_{ax}$, C-7H, C-8H).

2-Phenyl-2-(2-(5-ethyl-2-pyridyl)ethyl)indan ***28***

Cis- and *trans*-2-phenyl-2-(2-(5-ethyl-2-pyridyl)ethyl)indan-1,3-diol **25** (4 g, 11 mmol) were dissolved in methanol (100 mL) and concentrated hydrochloric acid (4 mL). Pd/C (5%, 0.4 g) was added and the mixture was hydrogenated at room temperature and atmospheric pressure until the required amount of hydrogen had been taken up (7 days). The catalyst was filtered off and the solvent was removed under reduced pressure. Saturated sodium bicarbonate was then added and the mixture was extracted with chloroform. The combined extracts were dried (Na_2SO_4) and the solvent was removed under reduced pressure to give an oil which solidified on standing. Recrystallization from ethanol gave *2-phenyl-2-(2-(5-ethyl-2-pyridyl)ethyl)indan* **28** as a white crystalline solid (2.3 g, 62%), mp 88–89°C. (Found: C 87.7, H 7.5, N 4.2%. $C_{24}H_{25}N$ requires C 88.1, H 7.6, N 4.3%.) ν_{max} (Nujol)/cm^{-1} 1600, 750. δ_H ($CDCl_3$) 6.9–8.3 (12H, ArH), 2.7 (4H, s, CH_2CH_2), 2.6 (2H, q, CH_2CH_3), 1.2 (3H, t, CH_2CH_3). *m/z* 327 (M^+).

2-Phenyl-2-(2-(2-piperidyl)methyl)indan-1,3-dione ***63***

2-Phenyl-2-(2-(2-pyridyl)methyl)indan-1,3-dione **62** (6 g, 19 mmol) was dissolved in glacial acetic acid and PtO_2 (0.5 g) was added. The mixture was hydrogenated on a Parr Hydrogenator until the calculated amount of hydrogen had been taken up. The mixture was filtered and the solvent removed under vacuum to give a thick oil. Saturated sodium bicarbonate solution was added until the mixture was basic, and the mixture was then extracted with chloroform. The combined extracts were dried (Na_2SO_4) and the solvent removed under vacuum to give *2-phenyl-2-(2-(2-piperidyl)methyl)indan-1,3-dione* **63** as a dark oil (4.1 g, 67%). (Found: C 78.9, H 6.4, N 4.4%. $C_{21}H_{15}NO_2$ requires C 79.0, H 6.6, N 4.4%.) ν_{max} (liquid film)/cm^{-1} 3300, 1760, 1710, 1600, 750. δ_H ($CDCl_3$) 7.2 (9H, ArH), 1.2–3.3 (12H, aliphatic).

*1,2,3,10b-Tetrahydro-10b-hydroxy-1-phenylpyrido[2,1-*a*]isoindol-6-(4*H*)-one* ***30***

2-Phenyl-2-(3-phthalimidopropyl)indan-1,3-dione **29** (20 g) was stirred and heated under reflux with hydrazine hydrate (6 mL) in ethanol (500 mL) for 1 h. The phthaldydrazide formed on cooling was filtered off and the filtrate evaporated to dryness. Chromatographic separation of the residue (10 g) over silica using diethyl ether as the elutant gave *1,2,3,10b-tetrahydro-10b-hydroxy-1-phenylpyrido[2,1-*a*]isoindol-6-(4*H*)-one* **30** as a white crystalline solid (3 g, 40%), mp 224–225°C. (Found: C 77.5, H 6.2, N 5.2%. $C_{18}H_{17}NO_2$ requires C 77.4, H 6.1, N 5.0%). ν_{max} ($CHBr_3$)/cm^{-1} 3560, 3320, 1680, 1600. λ_{max} (EtOH)/nm 261. δ_H [$(CD_3)_2SO$] 7.1–7.7 (8H, m, ArH), 6.5 (1H, s, OH), 6.3 (1H, d, ArH), 4.1 (1H, $J_{4ax,4eq}$ 12.5, $J_{4eq,3ax}$ 3.75, 4$_{eq}$-H), 3.15 (1H, $J_{4ax,4eq} = J_{4ax,3ax} = 12$, 4$_{ax}$-H), 2.5 (1H, m, 1$_{ax}$-H), 2.35 (1H, $J_{2ax,2eq} = J_{2ax,1ax} = J_{2ax,3ax} = 12.5$, $J_{2ax,3eq} = 3.75$, 2$_{ax}$-H), 1.6–2.0 (2H, m, 2$_{eq}$-H, 3$_{eq}$-H), 1.45 (1H, m, 3$_{ax}$-H).

A second fraction eluted with diethylether gave *2,3,4,4a-tetrahydro-4a-phenylindeno[1,2-b]pyridine-5-one* as a yellow crystalline solid (1.5 g), mp 95–96°C. (Found: C 82.9, H 5.9, N 5.4%. $C_{18}H_{15}NO$ requires C 82.7, H 5.8, N 5.4%). ν_{max} ($CDCl_3$)/cm^{-1} 1720, 1660, 1600. δ_H ($CDCl_3$) 7.2–8.2 (9H, m, ArH), 3.95 (2H, t, CH_2N), 2.4–2.8 (2H, m, C(Ph)CH_2), 1.45–2.2 (2H, m, $CH_2CH_2CH_2$). A third fraction eluted with diethylether gave *2,3-dihydro-1-phenyl-pyrido[2,1-*a*]isoindol-6(4*H*)-one* as a pale yellow crystalline solid (0.5 g), mp 142°C. (Found: C 82.6, H 5.9, N 5.3%. $C_{18}H_{15}NO$ requires C 82.7, H 5.8, N 5.4%).

*rel-(1*R*,10b*R*)-1,2,3,4,6-Hexahydro-1-phenylpyrido-[2,1-*a*]isoindole* ***33***

1,2,3,10b-Tetrahydro-10b-hydroxy-1-phenylpyrido[2,1-*a*]isoindol-6-(4*H*)-one **30** (2 g, 7.1 mmol) in tetrahydrofuran (THF; 50 mL) was added slowly to a stirred slurry of lithium aluminium hydride (0.5 g) in THF (25 mL). The mixture was heated and boiled under reflux for 30 h during which time the solution darkened. Water was carefully added and the solid precipitate filtered off and washed with chloroform. The solution was extracted with chloroform and the combined extracts were dried (Na_2SO_4). Removal of the solvent gave a thick dark oil. Chromatography over silica using diethylether as the elutant gave rel-*(1*R*,10b*R*)-1,2,3,4,6-hexahydro-1-phenylpyrido[2,1-*a*]isoindole* **33** as colourless needles (71 mg), mp 121–123°C. (Found: C 86.7, H 7.6, N 5.6%. $C_{18}H_{19}N$ requires C 86.7, H 7.7, N 5.6%). ν_{max} (Nujol)/cm^{-1} 1600, 750. δ_H ($CDCl_3$) 6.73–8.6 (9H, m, ArH), 4.2 & 3.55 (2H, AB, NCH_2Ar), 3.83 (1H, d, NCHCHPh), 3.55 (1H, m, CHPh), 3.19 (1H, m, NCH$_{eq}$), 2.57 (1H, m, NCH$_{ax}$). *m/z* 249 (M^+).

2-Phenyl-2-[2-(2-piperidyl)ethyl]phenalene-indan-1,3-dione ***36***

A solution of 2-phenyl-2-[2-(2-pyridyl)ethyl]phenalene-indan-1,3-dione **35** (2.1 g, 6.6 mmol) in absolute ethanol/water (50/50, 100 mL) and concentrated hydrochloric acid (1 mL) was hydrogenated in the presence of PtO_2 (Adam's catalyst) (0.25 g) at room temperature and atmospheric pressure until the required amount of hydrogen had been taken up. The catalyst was filtered off and the solvent was removed under reduced pressure to give an oil. Chromatography of this oil over alumina, using diethyl ether as the elutant gave *2-phenyl-2-[2-(2-piperidyl)ethyl]phenalene-indan-1,3-dione* **36** as a yellow oil (0.3 g). (Found: C 81.6, H 6.4, N 3.6%. $C_{26}H_{25}NO_2$ requires C 81.4, H 6.5, N 3.65%.) ν_{max} (Nujol)/cm^{-1} 3400, 1710, 1680, 1585. δ_H ($CDCl_3$) 7.3–8.1 (6H, m, ArH), 3.2 (1H, m, NCH$(CH_2)_2$), 3.0 (1H, dd, NCH$_{eq}$), 2.65 (1H, NCH$_{ax}$). *m/z* 383 (M^+), 278 ($M^+ - PhCO$).

*6-Phenyl-5,7-diketo-6-[2-(2-piperidyl)ethyl]dibenzo-[*a*,*c*]cycloheptane* ***39***

PtO_2 catalyst (0.25 g) was added to a solution of 6-phenyl-5,7-diketo-6-[2-(2-pyridyl)ethyl]dibenzo[*a*,*c*]cycloheptane **38** (0.75 g, 2 mL) in absolute ethanol (75 mL) and concentrated hydrochloric acid (0.3 mL) and the mixture was hydrogenated until the required amount of hydrogen had been taken up. The catalyst was filtered off and the solvent removed under reduced pressure to give an oil. The oil was added to aqueous

saturated sodium bicarbonate solution and the mixture was extracted with ethyl acetate. The combined extracts were dried (Na_2SO_4) and the solvent was removed under reduced pressure. Preparative thin layer chromatography over silica using ethyl acetate as the elutant gave *6-phenyl-5,7-diketo-6-[2-(2-piperidyl)ethyl]dibenzo[*a,c*]cycloheptane* **39** as an oil (30 mg). ν_{max} (Nujol)/cm^{-1} 1760, 1690. δ_H ($CDCl_3$) 7.2–7.9 (13H, m, ArH), 4.4 (1H, br s, NH), 0.8–3.9 (13H, m, aliphatic). Hydrogen gas was bubbled through the solution to give 6-phenyl-5,7-diketo-6-[2-(2-piperidyl)ethyl]dibenzo[*a*,*c*]cycloheptane hydrochloride. δ_H ($CDCl_3$) 9.0 (2H, br d, N^+H_2). *m/z* 409, 254.

*2,3-Dihydro-1-methylpyrrolo[2,1-*a*]isoindol-5-one **44***

2-Methyl-2-(2-*N*-phthalimodoethyl)-indan-1,3-dione **41** (20 g) was heated under reflux with hydrazine hydrate (3 mL) in ethanol (500 mL) for 1 h. A white gelatinous precipitate was rapidly produced and was decomposed by warming with excess dilute hydrochloric acid. The insoluble phthalhydrazide that formed was filtered off and washed with water. The filtrate was concentrated to remove ethanol and the cooled solution, after filtration from a further small amount of precipitated phthalhydrazide, was made alkaline with dilute sodium carbonate solution, and extracted with ethyl acetate. Solvent evaporation followed by repeated recrystallization of the residue from ethyl acetate gave *2,3-dihydro-1-methylpyrrolo[2,1-*a*]isoindol-5-one* **44** as a crystalline solid (3 g), mp 210–202°C. (Found: C 77.9, H 6.0, N 7.6%. $C_{12}H_{11}NO$ requires C 77.8, H 6.0, N 7.7%.) ν_{max} ($CDCl_3$)/cm^{-1} 1660, 1600. δ_H ($CDCl_3$) 7.3–8.0 (4H, m, ArH), 3.9 (2H, t, CH_2N), 3.1 (2H, m, CH_2CH_2N), 2.1 (3H, s, CH_3).

*1,2,3,10b-Tetrahydro-10b-hydroxy-1-methylpyrido-[2,1-*a*]isoindol-6(4*H*)-one **48**, **51**, **52***

2-Methyl-2-(3-*N*-phthalimidopropyl)-indan-1,3-dione **45** (26 g) was heated under reflux with hydrazine hydrate (4 mL) in ethanol (600 mL) for 2 h. The phthalhydrazide formed was filtered off and the solvent was removed by distillation to give a sticky foam (10 g). Dilute hydrochloric acid (2.5 mL) was added to a solution of the crude product (1 g) in ethanol (10 mL) and the mixture was heated over a water bath for 20 min. The solid that separated out was filtered off and the filtrate was basified with dilute sodium hydroxide. Extraction with ethyl acetate followed by recrystallization from ethanol gave *1,2,3,10b-tetrahydro-10b-hydroxy-1-methylpyrido[2,1-*a*]isoindol-6(4*H*)-one* **48** as a white crystalline solid (0.6 g), mp 212°C. (Found: C 71.9, H 7.0, N, 6.4%. $C_{13}H_{15}NO_2$ requires C 71.8, H 6.9, N 6.5%.) ν_{max} ($CHBr_3$)/cm^{-1} 3560, 1660, 1600. δ_H ($CDCl_3$) 7.2–7.7 (4H, m, ArH), 4.22 (1H, s, OH), 3.82 (1H, dm, C-4H$_{eq}$), 2.87 (1H, dt, C-4H$_{ax}$), 1.27 (3H, s, CH_3), 1.2–2.1 (5H, m, C-1H, C-2H, C-3H). The remainder of the crude hydrazinolysis product was chromatographed over Woelm alumina (grade III). The first fraction eluted with ether gave anti-*2,3,4,4a-tetrahydro-4a-methlyindeno-[1,2-*b*]pyridine-5-one hydrazone* **51** as a yellow crystalline solid (2 g), mp 125.5°C. (Found: C 73.2, H 7.1, N 19.7%. $C_{13}H_{15}N_3$ requires C 73.2, H 7.0, N 19.7%.) ν_{max} ($CDCl_3$)/cm^{-1} 3390, 1668, 1640, 1600. δ_H ($CDCl_3$) 7.8–8.15 (2H, m, ArH), 7.4–7.7 (2H, m, aromatic), 5.67–5.8 (2H, s, =N–NH_2), 3.9 (2H, t, –NCH_2(CH_2)$_2$), 1.5–2.2 (4H, m, NCH$_2$CH_2CH_2), 1.27 (3H, s, CH_3). A second fraction eluted with diethyl ether gave syn-*2,3,4,4a-tetrahydro-4a-methlyindeno-[1,2-*b*]pyridine-5-one hydrazone* **52** as a yellow crystalline solid (1 g), mp 148–149°C. (Found: C 73.4, H 6.9, N 19.7%. $C_{13}H_{15}N_3$ requires C 73.2, H 7.0, N 19.7%.) ν_{max} ($CDCl_3$)/cm^{-1} 3410, 3320, 1660, 1640, 1600. δ_H ($CDCl_3$) 7.3–7.8 (4H, m, ArH), 5.5 (2H, s, C=N–NH_2), 3.4–4.2 (2H, m, –NCH_2(CH_2)$_2$), 1.5–2.6 (4H, m, NCH$_2$CH_2CH_2), 1.4 (3H, s, CH_3).

*2,3,4,5-Tetrahydro-5a-methylindeno[1,2-*b*]azepin-6(5a*H*)-one **56***

2-Methyl-2-(4-*N*-phthalimidobutyl)-indan-1,3-dione **53** (0.5 g) was heated under reflux with hydrazine hydrate (0.1 mL) in ethanol (60 mL) for 45 min. The phthalhydrazide formed on cooling the reaction mixture was filtered off and dilute hydrochloric acid (10 mL) was added to the solution. The acidified solution was gently heated over a water bath for 15 min, and was filtered to remove the small quantity of additional phthalhydrazide residual that formed. The filtrate was made alkaline with dilute sodium hydroxide and extracted with ethyl acetate. Solvent evaporation afforded a yellow oil (0.2 g). Preparative thin layer chromatography using silica plates and diethyl ether afforded *2,3,4,5-tetrahydro-5a-methylindeno[1,2-*b*]azepin-6(5a*H*)-one* **56** as a yellow oil (0.1 g). (Found: C 78.8, H 7.1, N 6.6%. $C_{14}H_{14}NO$ requires C 78.9, H 7.0, N 6.6%.) ν_{max} ($CDCl_3$)/cm^{-1} 1705, 1660. δ_H ($CDCl_3$) 7.4–8.1 (4H, m, ArH), 4.2 (1H, dd, 2-H$_{eq}$), 3.75 (1H, t, 2-H$_{ax}$), 1.4–2.2 (6H, m, –$CH_2CH_2CH_2CH_2$N), 1.3 (3H, s, CH_3).

rel-*(3′*S*,1*S*,3*R*)-1-Phenyl-3-(piperidyl-2-yl)propylphthalide Hydrochloride **57***

Sodium borohydride (0.4 g) was added to a solution of rel-*(6*S*,8a*R*)-6-phenyl-6,7,8,8a,9,10,11,12-octahydropyrido[1,2-*b*][2]benzazonin-5,14-dione* **6** (1 g, 3 mmol) in dry methanol (25 mL) and the resulting mixture was stirred for one hour. The solvent was removed under reduced pressure and water (5 mL) was added followed by dilute hydrochloric acid until the solution was acidic. The remaining solution was extracted with ethyl acetate, the combined extracts were dried (Na_2SO_4) and the solvent was removed under reduced pressure to give a colourless oil. The oil was dissolved in ethyl acetate/ethanol (1/1) and left in an ice box overnight to yield white crystals. A further recrystallization gave rel-*(3′*S*,1*S*,3*R*)-1-phenyl-3-(piperidyl-2-yl)-propylphthalide hydrochloride* **57** as shiny white crystals (0.87 g, 86%), mp 242–244°C. (Found: C 71.1, H 7.1, N 3.8%. $C_{22}H_{26}NO_2Cl$ requires C 71.1, H 7.0, N 3.8%.) ν_{max} (Nujol)/cm^{-1} 3400, 1760, 1600. δ_H ($CDCl_3$) 9.45 (1H, br d, NH), 9.1 (1H, br d, NH), 6.4–7.8 (9H, m, ArH), 5.5 (1H, d, OCH), 3.1 (1H, br d, NCH$_{eq}$), 2.8 (1H, m, OCHCPhH), 2.8 (1H, m, NCH(CH_2)$_2$), 2.6 (1H, m, NCH$_{ax}$). *m/z* 335 (M^+), 202 (M^+ − PhCHCHCH_2CH(CH_2)$_4$NH), 133 (PhCOOCH), 105 (PhCO).

Accessory Materials

Syntheses and characterization data for **9**, **15**, **19**, **21**, **24**, **25**, **35**, **38**, **41**, **45**, **53**, **58**, **60**–**62** available from the authors or, until January 2011, the *Australian Journal of Chemistry*.

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