Two New Oxindole Syntheses†

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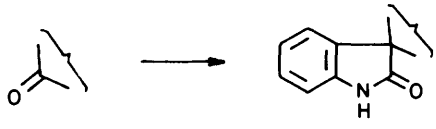
Two oxindole syntheses are described, both starting from ketones, in which the carbonyl carbon becomes C-3 of the oxindole. The first route uses *o*-lithioformanilide followed by attack with cyanide ion and hydrolysis. The second uses a pinacol-type rearrangement (or the γ-silyl alcohol variation) to create the quaternary centre, and involves an intramolecular displacement of fluoride ion from an unactivated benzene ring by an amide nitrogen to complete the lactam ring. The two routes are stereochemically complementary, giving different spiro-oxindoles from norbornanone.

Anticipating a need to convert a ketone (**1**) into the corresponding oxindole (**2**) we have developed two stereochemically complementary oxindole syntheses, which we reported in a preliminary communication.[1] We now report the experimental details of this work, enlarging the discussion, and including some results not mentioned earlier.

Results and Discussion

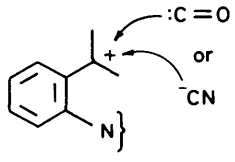
Whatever route one might devise to transform a ketone into an oxindole in the sense (**1**) ⟶ (**2**), two carbon atoms have to be



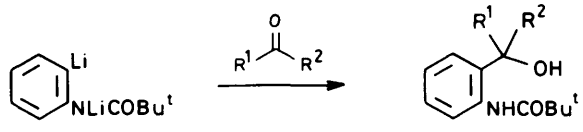
(**1**) (**2**)

bonded in succession to the carbonyl carbon atom. When the ketone (**1**) is prochiral, the order in which the two atoms are introduced should determine the stereochemistry of the oxindole: presumably the second carbon atom to be bonded to the carbonyl group would be on the less hindered face. (We use 'hindered' in this discussion without prejudice as to whether the hindrance is of steric or electronic origin.) For the synthesis of gelsemine,[2] the particular oxindole alkaloid we had in mind, we were not certain which face of the carbonyl group would be the less hindered, and so we needed to have in hand *two* routes, one in which the aryl group was on the less hindered side, the other in which the carbonyl carbon of the oxindole ring was on the less hindered side. The existing routes[3] and other potential routes[4] were ambiguous in this respect, and suffered from other drawbacks for the purpose we had in mind. Accordingly, we developed two routes, which are unambiguous and stereochemically complementary. We describe first the route which puts the carbonyl carbon of the oxindole ring on the less hindered side.

Route 1.—The key step in this route takes the form of attack by a carbon nucleophile on a carbonium ion (**3**). This cation should be available from the corresponding alcohol, and the alcohol should be available from the ketone and an aryl nucleophile with an *ortho* substituent that either already was a nitrogen function or could be converted into it. Accordingly,



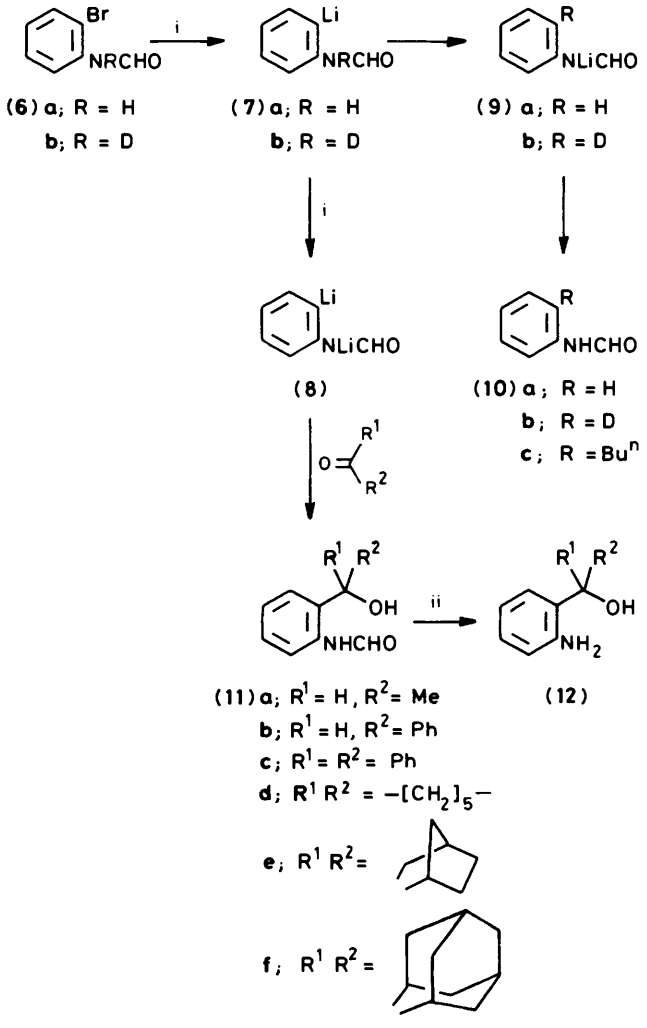
(**3**)



(**4**) (**5**)

our first need was to choose the aryl nucleophile. One attractive possibility was Gschwend's 2,*N*-dilithiopivalanilide (**4**),[5] prepared by *ortho* metallation of pivalanilide itself. This organolithium reagent had not been treated with aldehydes or ketones before, but we found that it did react with benzaldehyde and with adamantanone to give the amido alcohols (**5**), but in low yield because of the unavoidable presence of excess of butyllithium used to prepare the reagent (**4**). This can be avoided[6] by generating the dilithio reagent (**4**) from *o*-bromopivalanilide, but we were discouraged by the observation that the pivaloyl group was difficult to remove, and we turned therefore to a smaller group, the formyl. We were unable to metallate formanilide itself in the *ortho* position, and had to generate the lithio derivative (**8**) by halogen–metal exchange from *o*-bromoformanilide (**6a**). This was far from trouble-free, since halogen–metal exchange to a large extent preceded deprotonation of the amide, with the result that a substantial proportion of the first-formed intermediate (**7a**) quenched itself [(**7a**) ⟶ (**9a**)] to give, after work-up, formanilide (**10a**). Halogen–metal exchange taking place faster than deprotonation is not unknown.[7] We proved that this was indeed the problem by using the deuteriated starting material (**6b**) and treating it successively with excess of n-butyl-lithium, excess of benzaldehyde, and water. The formanilide produced, (**10b**), was heavily deuteriated at the *ortho* position. It is no solution to use an excess of butyllithium, since the excess will react with the ketone. However, we did find that lowering the temperature to −100 °C increased the amount of the *ortho*-lithio reagent (**8**), or conceivably (**7a**), available in the reaction mixture. This reagent reacted with acetaldehyde, benzaldehyde, benzophenone, cyclohexanone, norbornanone, and adamantanone to give the alcohols (**11**) in 37—61% yield, based on *o*-bromoformanilide. At this stage in our work it was appropriate to base the yield on

† No reprints available.



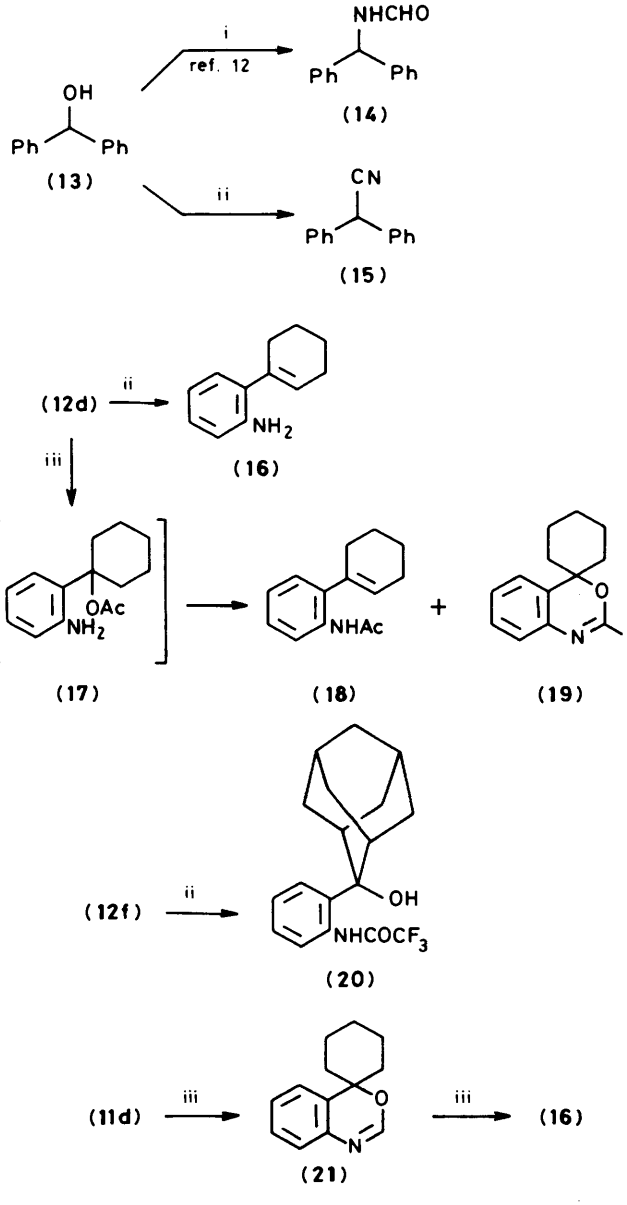
Scheme 1. *Reagents:* i, Bu^{n}Li; ii, KOH, MeOH

o-bromoformanilide, since this was the more expensive of the reaction partners. However, it gives a false impression of the effectiveness of the reagent. For the gelsemine synthesis, the ketone will be a very much more expensive component, and we shall be using the *o*-bromoformanilide in large excess, in order to have at least 1 mol equiv. of the effective reagent (**8**) present in the reaction mixture. To show that the reaction is in this sense high-yielding, we used successively 1, 2, and 3.8 mol equiv. of *o*-bromoformanilide (**6a**) with 1 mol equiv. of adamantanone and this raised the yield, *based on adamantanone*, successively from 56%, through 74%, to 85%.

More recently, Curran has shown[8] that the problem can be solved economically by treating *o*-bromoformanilide (**6a**) with 1 mol equiv. of sodium hydride before the halogen–metal exchange. (Our attempt to use this idea had foundered because we chose lithium hydride for this purpose, and the lithium salt precipitated.) We confirm the usefulness of Curran's method, and using it have prepared the product (**11f**) from adamantanone in 89% yield. Curran also used t-butyl-lithium, which avoids problems stemming from the presence of n-butyl bromide in our reaction mixture. Indeed, we have occasionally found *o*-n-butylformanilide (**10c**) in our product mixtures, but in our experience this has not been a serious problem, and we find the use of n-butyl-lithium to be more reliable. In any event our own work and Curran's have combined to overcome the initial difficulties, and to make the reagent (**8**) an easily available *o*-lithioaniline synthon.

Hydrolysis of the formyl group was easy. Potassium hydroxide in methanol converted each of the amido alcohols (**11**) into the corresponding amino alcohols (**12**) (Scheme 1); three of these compounds (**12a**—**c**) were known, and we prepared one of them, (**12b**), by the known route, to confirm our structural assignment. Acid-catalysed methanolysis was also easy but the products were not the amino alcohols (**12**). In the adamantyl case (**11f**), we isolated the methyl ether (**12f**; OMe for OH), and in the cyclohexyl case (**11d**) we isolated the cyclohexene (**16**). Curran has found that acidic hydrolysis of (**11d**) under slightly different conditions led to a practical synthesis of 3,4-tetramethylenequinoline.

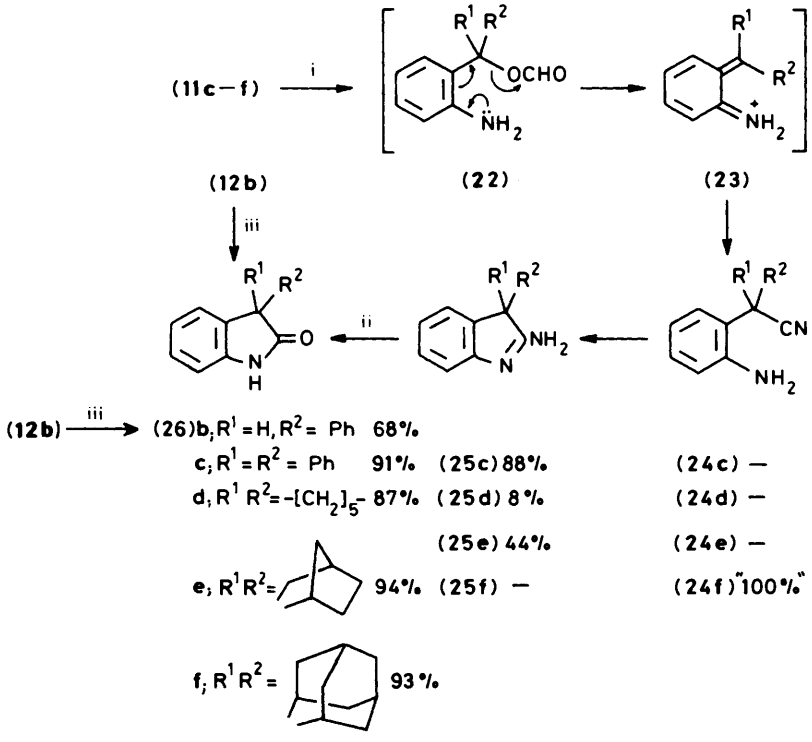
We were now ready to use the amino alcohols (**12**) as precursors for carbonium ions such as (**3**),[9] and to test whether cyanide ion or carbon monoxide would attack them. The hope was that the amino group would provide exceptional stabilisation, and that this stabilisation would deter the



Scheme 2. *Reagents:* i, HCN, BuOBu; ii, KCN, H_2SO_4, TFA; iii, KCN, AcOH

carbonium ion from rearrangement. The formation of the ether (**12f**; OMe for OH) was already a promising sign, and even better was the formation of a similar ether (**12f**; OEt for OH) during an attempt to recrystallise (**12f**) from ethanol. We tried carbon monoxide first, adding the amino alcohol (**12b**) to a mixture of sulphuric and formic acids in a Koch–Haaf reaction.[10] We isolated directly 3-phenyloxindole (**26b**), identical with an authentic sample, in 68% yield. Unfortunately, this was our only success with carbon monoxide, so we turned to cyanide ion. This nucleophile had the disadvantage that it might react with the intermediate carbonium ion from the nitrogen end of the ambident nucleophile, to give the formamide in a Ritter reaction.[11] Thus benzhydrol (**13**) is reported[12] to give *N*-(diphenylmethyl)formamide (**14**) with hydrogen cyanide in dibutyl ether. As it happens, using potassium cyanide and sulphuric acid in trifluoroacetic acid (TFA), we find the product to be diphenylacetonitrile (**15**), but we were not able to use identical reaction conditions to those of the earlier workers, because they do not report them. Armed with this promising result, and with the knowledge that the stabilisation of the cation by the *ortho* amino group should make the Ritter reaction even less favourable, we tried cyanide ion on the amino alcohols (**12d**) and (**12f**). The amino alcohol (**12d**) with potassium cyanide and sulphuric acid in TFA gave only the aminophenylcyclohexene (**16**), and with potassium cyanide in acetic acid it gave a mixture of the amide (**18**) and the benzoxazine (**19**). It seems likely that the carbonium ion is formed, but it does not capture cyanide ion; either it loses a proton to give (**16**) or it is attacked by acetate ion to give the ester (**17**), from which the amide (**18**) was produced by intramolecular acyl transfer. Similarly, in the adamantyl series, the amino alcohol (**12f**) gave the trifluoroacetamide (**20**) (Scheme 2),

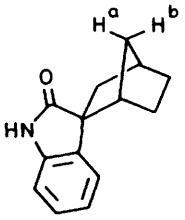
For a solution to this problem, we considered the possibility that the ester–amide exchange, observed above, might be reversible, and that the *esters* of the amino alcohols (**12**) might be precursors of the carbonium ion (**3**). Mild treatment of the formamido alcohol (**11d**) with potassium cyanide in acetic acid gave the benzoxazine (**21**) in a precedented reaction.[8,13] Under more vigorous conditions, the product was the aminocyclohexene (**16**). While the capture of cyanide had not occurred in this sequence, the isolation of an *amino*cyclohexene showed that we did not need to use the amino alcohols (**12**) as substrates for the cation (**23**); we could use the amido alcohols (**11**) directly and strong acid might be unnecessary. Indeed, in the base-catalysed hydrolyses (**11**) ⟶ (**12**), we had observed the formation of a less polar by-product, which was best explained by this route: we isolated the by-product (22%) only in the adamantyl series, and found it to be the ether (**12f**; OMe for OH). Evidently, the formyl group could be transferred from *N* to *O* [(**11**) ⟶ (**22**)] and the formate, with the help of the *ortho* amino group, was a good enough leaving group to give the cation (**23**). Eventually, we found conditions in which cyanide was captured: thus, the formamido alcohol (**11f**) with sodium cyanide for 1—6 days at 80 °C in dimethylformamide (DMF) gave the amino nitrile (**24f**) in essentially quantitative yield. In the presence of base, or when tetrabutylammonium cyanide was used, we obtained the aminoindolenine (**25f**) instead. When we used the formamido alcohol (**11c**) we could isolate only the aminoindolenine (**25c**) in 88% yield. Clearly, the reaction was excellent for those amido alcohols derived from non-enolisable ketones. The amido alcohol (**11b**) derived from benzaldehyde did not give any product derived from cyanide capture. With the amido alcohols (**11d**) and (**11e**), derived from enolisable ketones, we had a serious by-product, which greatly reduced the yield. The aminoindolenines (**25d** and **e**) were formed in only 8 and 44% yield, and the major products were the aminophenylcyclohexene (**16**) and the corresponding norbornene, respectively. These products are a consequence of easy proton loss from the cation (**23**), which might be initiated by a [1,5]-sigmatropic shift to nitrogen. Since gelsemine was to be prepared from a non-enolisable ketone we did nothing to avoid this problem. We simply hydrolysed the aminoindolenines (**25**) by heating their hydrochlorides in water.[14] The oxindoles (**26c**)



Scheme 3. *Reagents:* i, NaCN, DMF; ii, HCl, H_2O; iii, HCO_2H, H_2SO_4

and **26d**) were identical (mixed m.p., i.r., ^{1}H n.m.r.) with authentic samples.[15,16] In the adamantanone series, we hydrolysed the crude amino nitrile (**24f**) in the same way, and thus prepared the oxindole (**26f**) directly in 93% yield. *Thus, the overall yield of the oxindole* (**26f**) *from adamantanone, in the only sequence for which we worked out the best conditions, was a remarkable 83%.* These reactions are shown in Scheme 3.

In the norbornane series, the formamido alcohol (**11e**), the aminoindolenine (**25e**) and the oxindole (**26e**) were single compounds. We assume that the formamido alcohol (**11e**) has the aryl group *exo*, and we confirmed that the oxindole (**26e**), which we call the Wallace oxindole,[1] has the carbonyl group of the oxindole ring *exo*: irradiation of H^a in the Wallace oxindole (**26e**) caused a significant enhancement only in the signal from H^b. This stereochemistry corresponds to capture of the cyanide ion from the *exo* direction.

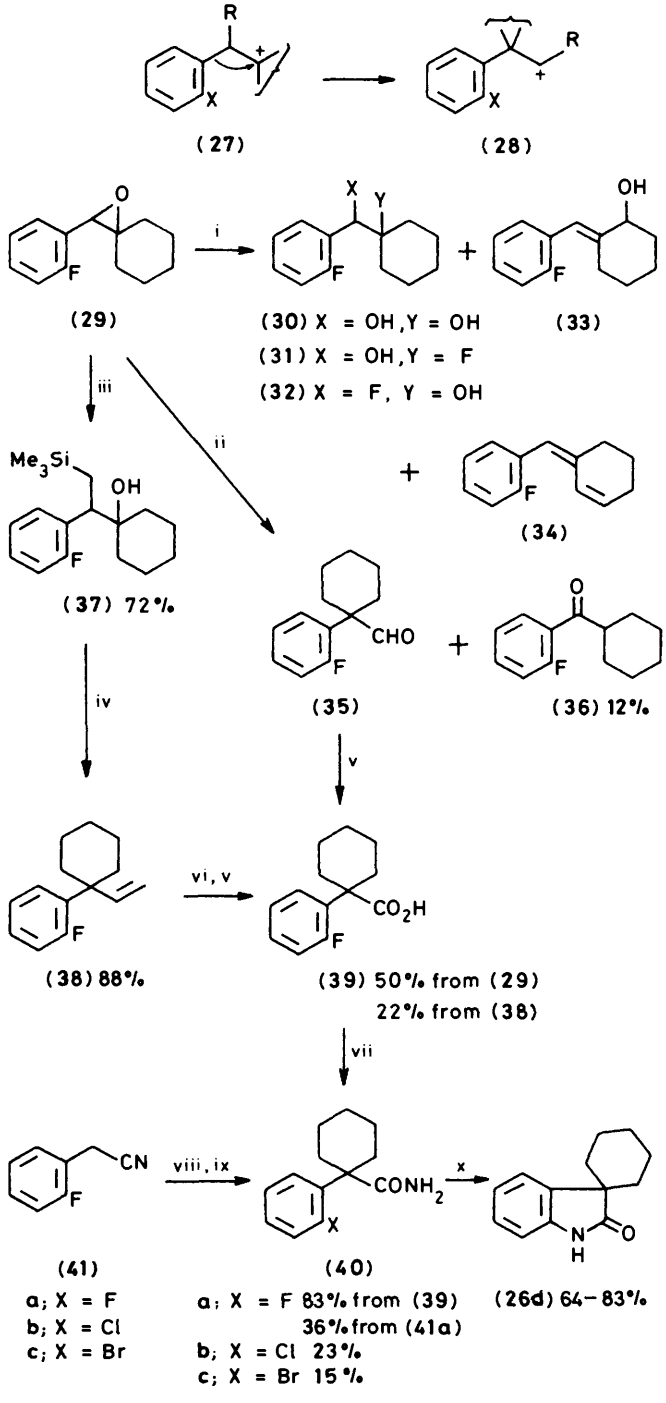


(**26e**)

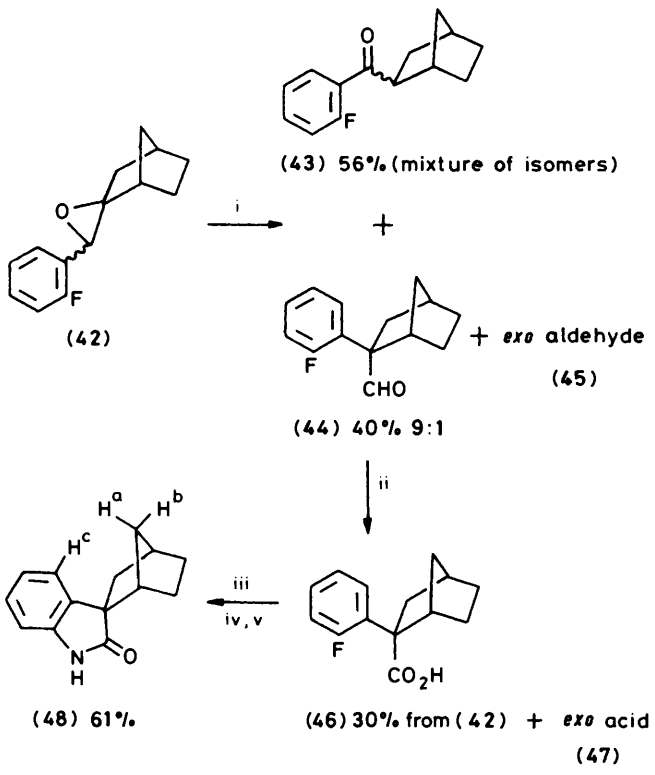
Route 2.—The key step in this route involves the migration (**27**) ⟶ (**28**) of an aryl group to a carbonium ion centre. We had to choose a group X to mark the position of the amino group of the oxindole ring, and a group R which would encourage rearrangement by stabilising the product cation (**28**). In considering what X might be, we feared that an amino group would capture the cation (**27**) intramolecularly, and that a nitro group would discourage migration (**27**) ⟶ (**28**). For these reasons, we chose halogen for X, and fluorine in particular, on the grounds that it would interfere least with the migration step (it has the highest (*o* + *p*)/*m* ratio in electrophilic substitution of the halogenobenzenes[17]), while not being resistant to aromatic nucleophilic substitution by the addition–elimination route.[18]

Working in the cyclohexyl series first, we easily prepared the epoxide (**29**) by Wittig reaction and epoxidation. However, we had difficulty finding the best conditions for carrying out the pinacol–pinacolone type of rearrangement, even though it had already been studied[19] for the unsubstituted compound (*i.e.* lacking the fluorine atom). We detected seven different products under various conditions, including the products of nucleophilic capture of water, (**30**), and, somewhat unusually, of fluoride ion, (**31**) and (**32**) (using boron trifluoride–diethylether as catalyst), the dehydration products (**33**) and (**34**), and the desired aldehyde (**35**) mixed with the hydride-shift product (**36**). After much experimentation we found conditions ($AlCl_3$; CH_2Cl_2; −55 °C; 30 min; room temp.) in which the aldehyde and ketone were the major products (91% yield) in the ratio 4:1). Oxidation of the mixture converted the aldehyde into the acid (**39**), which made separation easy. The overall yield of acid from the epoxide (**29**) was 50%.

In view of these difficulties, we also tried a silicon-controlled rearrangement, since we have already established[20] how similar trimethylsilylethyl alcohols were to pinacols in their rearrangements. We reported this part of our work in a separate preliminary communication.[21] This silicon-controlled rearrangement proved to be easy: trimethylsilylmethylmagnesium chloride with copper catalysis opened the epoxide (**29**) to give the alcohol (**37**). This alcohol cleanly gave the vinylcyclohexane (**38**) in 88% yield, and the vinyl group could be oxidised to give the acid (**39**). The extra step actually made the overall yield lower in this route. The advantage it possesses is only that the conditions for carrying out the transformation (**37**) ⟶ (**38**) were much easier to find than the conditions for the pinacol type of transformation (**29**) ⟶ (**35**). The acid (**39**) gave an amide (**40a**) and this cyclised on treatment with base to give the oxindole (**26d**), identical with an authentic sample. These reactions are shown in Scheme 4.



Scheme 4. *Reagents:* i, Various acidic reagents; ii, $AlCl_3$; iii, Me_3SiCH_2MgCl, CuCl; iv, TFA; v, CrO_3; vi, O_3; vii, $SOCl_2$, NH_3; viii, KOH, $Br[CH_2]_5Br$; ix, H_2SO_4, AcOH; x, LiH, DMF



Scheme 5. *Reagents:* i, TFA; ii, CrO_3; iii, $SOCl_2$; iv, NH_3; v, LiH, DMF

We have investigated this cyclisation in more detail since our preliminary communication.[1] There, we reported a 39% yield using sodium hydride in diglyme [bis-(2-methoxyethyl) ether] for 24 h under reflux. We now find that lithium hydride in DMF at 135—140 °C gives the oxindole in 77% yield. We were intrigued to know whether fluoride was the best halide to have chosen for this step. Accordingly, we synthesised each of the amides (**40a**—**c**) by a shorter route (**41**) ⟶ (**40**), and subjected each to the latter cyclisation conditions. In each case, the oxindole (**26d**) was produced in good yield: X = F 77%, X = Cl 64%, and X = Br 83%. It appears that there is no special advantage for this step to have fluoride as the leaving group.

Finally, we tested this route on norbornan-2-one, in order to check whether it could be relied upon to deliver the aryl group to the less hindered surface. We made the mixture of epoxides (**42**) in two steps from norbornanone and tried first to carry out the rearrangement using the comparatively well behaved silicon-controlled route. Trimethylsilylmethylmagnesium chloride, and copper(I) catalysis, opened the epoxide to give a mixture of stereoisomeric γ-silyl alcohols, but acid-catalysed rearrangement gave rise largely to hydride shift, in contrast to all our earlier work where aryl shift occurred. Accordingly, we had to return to straightforward, acid-catalysed rearrangement of our epoxide (**43**), but even here, under the best conditions we could find, hydride shift was the major pathway, and gave the ketones (**43**) in 56% yield. The aldehydes (**44**) and (**45**) were present in the ratio 5:1 in only 40% yield. We oxidised the mixture of ketones and aldehydes to a mixture of ketones and acids, at which stage we easily separated the acids from the ketones, and then separated the major acid (**46**) from the minor one (**47**) by fractional crystallisation. The overall yield of the acid (**46**) was 30%. The remaining steps, amide formation and cyclisation (using the conditions which at that time had not been optimised), gave the oxindole (**48**) (Scheme 5) which proved to be different from the earlier oxindole (**26e**). Irradiation of H^a in this oxindole (**48**), which we call the Loreto oxindole,[1] showed nuclear Overhauser enhancement in both H^b and H^c, confirming the stereochemical assignments to the two oxindoles.

Route 2 is much less efficient than Route 1, because of the difficulty in controlling the cationic rearrangement. It also appears likely that there is some difficulty in persuading an aryl group to migrate towards a relatively hindered cationic centre. On the other hand, Route 2 does not suffer from the limitation that Route 1 has with respect to proton loss [(**12d**) ⟶ (**16**)]. The two routes therefore have complementary features both in their structural limitations and in their stereochemical outcome.

Experimental

Light petroleum refers to the fraction boiling in the range 60—80 °C.

General Method for Preparation of o-Formamidobenzyl Alcohols (**11**).—n-Butyl-lithium (12.4 ml of a 1.6M solution in hexane, 20 mmol) was added to a stirred solution of dry *o*-bromoformanilide[22] (2.00 g, 10 mmol) in tetrahydrofuran (THF), at a rate which kept the temperature below −100 °C. The mixture was then kept at −110 °C for 3 h, when no *o*-bromoformanilide remained (t.l.c.). A solution of the necessary carbonyl compound (9.5 mmol) in dry THF (10 ml) was introduced at −105 °C and the mixture was kept at this temperature for 1 h, then at −78 °C for 3 h. Saturated aqueous ammonium chloride (20 ml) was added and the mixture was warmed to room temperature, separated, and extracted with ether (3 × 10 ml) and the combined extracts were washed with saturated brine, dried ($MgSO_4$), and evaporated under reduced pressure. The crude reaction product was triturated with light petroleum to give the amido alcohols (**11**). The following amido alcohols were prepared in this way. *2-Formamidodiphenylmethanol* (**11b**) (62%), prisms, m.p. 121—122 °C (from toluene) (Found: C, 73.8; H, 5.7; N, 6.1. $C_{14}H_{13}NO_2$ requires C, 74.0; H, 5.70; N, 6.2%); $\nu_{max.}$(Nujol) 3 380, 3 290, 1 678, and 1 520 cm^{-1}; $\delta_H(CDCl_3)$ 9.70—9.40 (1 H, br m, N*H*CHO *E* and *Z* rotamers), 8.36 (0.3 H, d, *J* 12 Hz, NHC*H*O *E*), 8.28 (0.7 H, s, NHC*H*O *Z*), 7.84 (0.7 H, d, *J* 7 Hz, *o*-ArH *Z*), 7.52—7.00 (8 H, m, Ph and 3 × ArH), 6.54—5.96 (1 H, br, OH), and 5.96 (1 H, s, C*H*Ph); *m/z* 227 (25%, M^+), 209 (15, $M - H_2O$), 198 (25, M − CHO), 182 (50, $M - HCO_2$), 181 (25, $M - HCO_2H$) and 180 (100, 209 − HCO).

2-Formamidotriphenylmethanol (**11c**) (56%), plates, m.p. 178—179 °C (from toluene–ethyl acetate) (Found: C, 79.0; H, 5.6; N, 4.5. $C_{20}H_{17}NO_2$ requires C, 79.2; H, 5.60; N, 4.6%); $\nu_{max.}$(Nujol) 3 430, 3 300, 1 670, and 1 525 cm^{-1}; δ_H [$CDCl_3$ + $(CD_3)_2SO$] 9.68—9.20 (1 H, br m, N*H*CHO *E* and *Z*), 8.24, (0.7 H, dd, *J* 8 and 2 Hz, *o*-ArH *Z*), 8.15 (0.3 H, d, *J* 12 Hz, NHC*H*O *E*), 7.91 (0.7 H, d, *J* 2 Hz, NHC*H*O *Z*), 7.25 (11 H, s, 2 × Ph + OH), and 7.11—6.50 (3.3 H, m, ArH); *m/z* 303 (30%, M^+), 285 (15, $M - H_2O$), and 256 (100, 285 − CHO).

1-(2-Formamidophenyl)cyclohexan-1-ol (**11d**) (55%), plates, m.p. 143—144 °C (from toluene) (Found: C, 71.2; H, 7.5; N, 6.4. $C_{13}H_{17}NO_2$ requires C, 71.2; H, 7.75; N, 6.4%); $\nu_{max.}$(Nujol) 3 310, 3 230, 1 675, and 1 520 cm^{-1}; $\delta_H(CDCl_3)$ 10.20—9.60 (1 H, br d, *J* 11 Hz, N*H*CHO *E* and *Z*), 8.55 (1 H, d, *J* 11.5 Hz, NHC*H*O *E* and *Z*), 8.31 (0.7 H, d, *J* 7.5 Hz, *o*-ArH *Z*), 6.94—7.44 (3.3 H, m, ArH), 2.66 (1 H, s, OH), and 2.32—1.08 (10 H, br m, 5 × CH_2); *m/z* 219 (95%, M^+), 201 (60, $M - H_2O$), and 149 (100, $M - C_5H_{12}$).

2-exo-(*2-Formamidophenyl*)-2-endo-*norborneol* (**11e**) (37%),

plates, m.p. 124—126 °C (from toluene–light petroleum) (Found: C, 72.7; H, 7.25; N, 6.1. $C_{14}H_{17}NO_2$ requires C, 72.7; H, 7.35; N, 6.1%); $\nu_{max.}$(Nujol) 3 250, 1 680, and 1 520 cm^{-1}; δ_H [$(CD_3)_2SO$] 8.80—8.54 (1 H, NHCHO *E* and *Z*), 8.40 (0.4 H, d, *J* 11 Hz, NHC*HO E*), 8.22 (0.6 H, d, *J* 1.5 Hz, NHC*HO Z*), 8.06 (0.6 H, dd, *J* 7 and 1 Hz, *o*-ArH *Z*), 7.46—6.92 (3.4 H, m, ArH), 2.80 (1 H, d, *J* 9.5 Hz, bridgehead H), 2.48 (1 H, s, OH), 2.40—1.90 (3 H, m, bridgehead H and RCHCH_2R), and 1.89—1.30 (6 H, m, 3 × CH_2); *m/z* 235 (100%, M^+) and 217 (50, $M - H_2O$).

2-(2-*Formamidophenyl*)*adamantan*-2-*ol* (**11f**) (56%), fine prisms, m.p. 213—213.5 °C (from ethyl acetate) (Found: C, 75.0; H, 7.45; N, 5.4. $C_{17}H_{21}NO_2$ requires C, 74.7; H, 7.40; N, 5.5%); $\nu_{max.}$(Nujol) 3 300, 1 670, and 1 520 cm^{-1}; δ_H [$(CD_3)_2SO$] 9.01 (0.4 H, br m, NHCHO *E*), 8.39 (0.6 H, s, NHCHO *Z*), 8.11 (0.6 H, s, NHC*HO Z*), 8.00 (0.6 H, dd, *J* 7 and 2 Hz, *o*-ArH *Z*) 7.58—6.87 (4 H, m, 3 × ArH and NHC*HO E*), 5.50 (1 H, m, OH), 3.28 (1 H, s, bridgehead H), 2.50 (4 H, m, 2 × bridgehead H, adjacent to quaternary centre and 2 × H 1,3 diaxial with respect to the OH), and 1.73 (9 H, m, 3 × CH and 3 × CH_2).

The following compound was made in the same way but was isolated by chromatography on silica gel with methanol–methylene dichloride (5:95) as eluant; 1-(2-*formamidophenyl*)-*ethanol* (**11a**) (53%), an oil, $\nu_{max.}$(neat) 3 300, 1 680, and 1 520 cm^{-1}; δ_H($CDCl_3$) 10.0 (0.6 H, br s, NHCHO *Z*), 9.15 (0.4 H, br d, NHCHO *E*), 8.55 (0.4 H, d, *J* 11 Hz, NHC*HO E*), 8.35 (0.6 H, s, NHC*HO Z*), 8.10 (0.6 H, d, *J* 7 Hz, *o*-ArH *Z*), 7.35—6.90 (3.4 H, m, ArH), 4.95 (1 H, q, *J* 6 Hz, ArC*H*Me), 2.50 (1 H, m, OH), and 1.60 (3 H, d, *J* 6 Hz, ArCHMe) (Found: M^+, 165.0789. $C_9H_{11}NO_2$ requires *M*, 165.0789); *m/z* 165 (50%) and 132 [100, $M - H_2O + CH_3$)].

Optimum Preparation of the Alcohol (**11f**).—(Experiment carried out by Dr. M. Honan) *o*-Bromoformanilide [22] (859 mg, 4.29 mmol) was stirred with oil-free sodium hydride (250 mg of a 50% suspension, 5.21 mmol) in THF (2 ml) at room temperature for 0.5 h. n-Butyl-lithium (5.4 ml of a 1.6M solution in hexane, 8.67 mmol) was added at −78 °C during 10 min, followed by hexamethylphosphoric triamide (0.9 ml). After 30 min, a solution of adamantanone (620 mg, 4.13 mmol) in THF (2 ml) was added during 10 min, and the mixture was stirred for a further 1 h at −78 °C. Aqueous work-up and crystallisation from ethyl acetate as before gave the alcohol (**11f**) (856 mg), and flash chromatography of the mother liquors gave a further crop (143 mg, total yield 89%).

Metallation of N-*Deuterio*-o-*bromoformanilide* (**6b**).—n-Butyl-lithium (9.6 ml of a 1.61M solution in hexane, 14.9 mmol) was added slowly to a stirred, chilled solution of the labelled anilide (**6b**) [1.502 g, 7.45 mmol, prepared by repeated washing of a chloroform solution of the unlabelled anilide (**6a**) with 1M-potassium hydroxide in deuterium oxide] in dry THF (40 ml) under nitrogen, while the temperature was kept below −60 °C. After 4 h at −78 °C, a solution of benzaldehyde (0.844 g, 7.96 mmol) in dry THF (10 ml) was added, and the mixture was kept at −78 °C for a further 2 h. Work-up as before gave α-(2-formamidophenyl)benzyl alcohol (0.546 g, 32%). Distillation of the mother liquors (bulb-to-bulb) and chromatography (SiO_2; 10% MeOH in $CHCl_3$) gave crude formanilide (0.024 g), m.p. 40—42 °C (lit.,[23] 50 °C); δ_H [$CDCl_3$ + 0.4 mol equiv. [$^2H_4$]Eu(fod)$_3$] 13.8 (0.26 H, s, NHC*HO Z*), 12.7 (0.74 H, br m, NHCHO *E*), 11.0 (0.28 H, m, *o*-ArH *Z*), 9.80 (0.26 H, s, NHCHO *Z*), 8.25 (1.63 H, d, *J* 7 Hz, *o*-ArH and NHC*HO E*), and 7.95—7.40 (3 H, m, ArH) (Found: M^+, 122.0595. C_7H_6DNO requires *M*, 122.0591); *m/z* 122 (100%), 121 (40, PhNHCHO), 94 (60, $M - CO$), 67 (35, 94 − HCN), and 66 (30, 94 − DCN).

Hydrolysis of the Formamido Alcohols in Methanol.—A solution of a formamido alcohol (**11**) (1—3 mmol) in methanolic aqueous potassium hydroxide (5—15 ml of a 1.2M solution) was refluxed under nitrogen for 1.5 h. The methanol was evaporated off and the residue was suspended in water (20 ml) and extracted with ethyl acetate (3 × 10 ml). The combined extracts were dried ($MgSO_4$) and evaporated and the residue was crystallised to give the following amino alcohols. 1-(2-Aminophenyl)ethanol (**12a**) (61%), needles, m.p. 48—50 °C (from light petroleum) (lit.,[24] 54—59 °C) δ_H($CDCl_3$) 7.05 (2 H, m, ArH), 6.75 (2 H, m, ArH), 4.87 [1 H, q, *J* 6 Hz, ArC*H*(OH)Me], 3.60 (3 H, br s, OH and NH_2), and 1.55 [3 H, d, *J* 6 Hz, ArCH(OH)Me] (Found: M^+, 137.0829. Calc. for $C_8H_{11}NO$: *M*, 137.0841); *m/z* 137 (100%), 119 ($M - H_2O$), and 69 (100).

2-Aminodiphenylmethanol (**12b**) (89%), prisms, m.p. 110—112 °C (from aqueous ethanol) (lit.,[25] 120 °C), identical (mixed m.p., i.r., and ^1H n.m.r.) with an authentic sample.

2-Aminotriphenylmethanol (**12c**) (53%), needles, m.p. 114—115 °C (from light petroleum) (lit.,[26] 121 °C); $\nu_{max.}$(Nujol) 3 440, 3 390, 3 340, 3 080, 3 060, 3 040, and 1 620 cm^{-1}; δ_H($CDCl_3$) 7.60—6.95 (2 H, m, ArH), 7.25 (10 H, s, 2 × Ph), 6.80—6.30 (2 H, m, ArH), and 3.95 (3 H, br, m, OH and NH_2) (Found: M^+ 275.1342. Calc. for $C_{19}H_{17}NO$: *M*, 275.1310); *m/z* 275 (1.5%) and 257 (100, $M - H_2O$).

1-(2-*Aminophenyl*)*cyclohexan*-1-*ol* (**12d**) (85%), needles, m.p. 92—94 °C (from light petroleum) (Found: C, 75.2; H, 9.05; N, 7.3. $C_{12}H_{17}NO$ requires C, 75.4; H, 8.90; N, 7.3%); $\nu_{max.}$(Nujol) 3 510, 3 425, 3 355, and 1 625 cm^{-1}; δ_H($CDCl_3$) 7.26—6.90 (2 H, m, ArH), 6.74—6.52 (2 H, m, ArH), 3.46 (3 H, br m, NH_2 and OH), 2.14 (2 H, m, 2 × 3-H_{ax}), 1.70 (6 H, m, cyclohexyl), and 1.24 (2 H, m, 2 × 3-H_{eq}); *m/z* 191 (35%, M^+) and 173 (100, $M - H_2O$).

2-exo-(2-*Aminophenyl*)-2-endo-*norborneol* (**12e**) (67%), needles, m.p. 115.5—116.5 °C (from light petroleum) (Found: C, 76.6; H, 8.4; N, 7.0. $C_{13}H_{17}NO$ requires C, 76.8; H, 8.40; N, 6.9%); $\nu_{max.}$(Nujol) 3 410, 3 310, 3 240, and 1 615 cm^{-1}; δ_H($CDCl_3$) 7.34—6.90 (2 H, m, ArH), 6.82—6.54 (2 H, m, ArH), 3.48 (3 H, br m, OH and NH_2), 2.78 (1 H, br s, bridgehead H), 2.25 (1 H, br s, bridgehead H), 2.20 (2 H, m, CH_2), and 1.86—1.26 (6 H, m, 3 × CH_2); *m/z* 203 (40%, M^+) and 185 (100, $M - H_2O$).

2-(2-*Aminophenyl*)*adamantan*-2-*ol* (**12f**).—This was prepared in the same way, but chromatography (SiO_2; 10% methanol in chloroform) gave the *amino alcohol* (**12f**) (53%) as prisms, m.p. 88—89 °C (from light petroleum); R_F (10% MeOH in $CHCl_3$) 0.53; $\nu_{max.}$(Nujol) 3 375, 3 280, and 1 605 cm^{-1}; δ_H($CDCl_3$) 7 30 (1 H, br d, *J* 8 Hz, *o*-ArH), 7.0 (1 H, br d, *J* 8 Hz, *o*-ArH), 6.7 (2 H, br t, *J* 8 Hz, 2 × ArH), 3.45 (3 H, m, OH and NH_2), 2.75 (2 H, m, 2 × bridgehead H), 2.45 (2 H, br d, *J* 15 Hz, 2 × 3-H *cis* to OH [27]), 1.83 and 1.70 (8 H, 2 × m, CH and CH_2), and 1.65 (2 H, br d, 2 × 3-H *trans* to OH [27]) (Found: M^+, 243.1609. $C_{16}H_{21}NO$ requires *M*, 243.1623); *m/z* 243 (20%) and 225 (100, $M - H_2O$), and 2-(*aminophenyl*)-2-*methoxyadamantane* (22%), an oil, R_F (10% MeOH in $CHCl_3$) 0.89; $\nu_{max.}$(neat) 3 450, 3 350, 1 605, and 1 610 cm^{-1}; δ_H($CDCl_3$) 7.35—6.90 (2 H, m, ArH), 6.80—6.50 (2 H, m, ArH), 4.30 (2 H, m, NH_2), 3.07 (1 H, br m, bridgehead H), 2.84 (3 H, s, OMe), 2.57 (1 H, br m, bridgehead H), 2.39 (2 H, d, *J* 14 Hz, 2 × 3-H *cis* to OMe [27]), 2.20 (1 H, m, bridgehead H), 2.00—1.65 (7 H, br m, CH and 3 × CH_2), and 1.50 (2 H, br d, *J* 14 Hz, 2 × 3-H *trans* to OMe [27]) (Found: M^+, 257.1784. $C_{17}H_{23}NO$ requires *M*, 257.1780); *m/z* 257 (10%), 226 (25, $M - CH_3O$), and 225 (100, $M - CH_3OH$). The ether by-product was avoided when the formamide (1.6 mmol) was refluxed with aqueous potassium hydroxide (7 ml; 5%) in dioxane (15 ml) for 16 h, when the amino alcohol was produced in 71% yield.

Recrystallisation of 2-(2-*Aminophenyl*)*adamantan*-2-*ol* (**12f**) *from Aqueous Ethanol.*—The crude amino alcohol (**12f**) (0.542 g

from an earlier run) was dissolved in warm ethanol, and enough water was added to cause faint turbidity. As the mixture cooled, an oil separated; more water (25 ml) was added and the mixture was extracted with ether (3 × 10 ml). The extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give an oil (0.44 g) which was chromatographed (SiO_2; CH_2Cl_2) to give the amino alcohol (**12f**) (0.416 g, 33%) and 2-(2-*aminophenyl*)-2-*ethoxyadamantane* (0.137 g, 28%), needles, m.p. 78—79 °C (from aqueous ethanol); R_F 0.79 (33% ethyl acetate–toluene); $\nu_{max.}$(Nujol) 3 450, 3 350, and 1 620 cm^{-1}; $\delta_H(CCl_4)$ 7.20—6.25 (2 H, m, ArH), 6.65—6.35 (2 H, m, ArH), 4.30 (2 H, br m, NH_2), 3.30 (1 H, dq, *J* 14 and 7 Hz, OCH_AH_BMe), 3.12 (1 H, br m, bridgehead H), 2.85 (1 H, dq, *J* 14 and 9 Hz, $OCH_AH_BCH_3$), 2.58 (1 H, m, bridgehead H), 2.38 (2 H, br d, *J* 11 Hz, 2 × 3-H *cis* to O[27]), 2.20 (1 H, m, bridgehead H), 2.00—1.62 (7 H, m, CH and 3 × CH_2), 1.54 (2 H, br d, *J* 11 Hz, 2 × 3-H *trans* to O), and 1.15 (3 H, dd, *J* 9 and 7 Hz, OCH_2Me).

2-(*Cyclohex*-1-*enyl*)*aniline* (**16**).—A solution of the formamido alcohol (**11d**) (0.051 g, 0.23 mmol) in ethanol (3 ml) was refluxed with dil. hydrochloric acid (3 ml; (6M) under nitrogen for 45 min. The mixture was poured into aqueous potassium hydroxide (10 ml; 2%), and worked up (EtOAc) to give the amine (**16**) (0.023 g, 57%) as an oil (lit.,[28] b.p. 125 °C/25 mmHg), $\nu_{max.}$(neat 3 350, 3 340, 3 050, 1 610, and 810 cm^{-1}; $\delta_H(CDCl_3)$ 6.83 (2 H, m, ArH), 6.52 (2 H, m, ArH), 5.64 (1 H, br m, =CH), 3.46 (2 H, m, NH_2), 2.17 (4 H, m, CH_2C=$CHCH_2$), and 1.70 (4 H, m, 2 × CH_2) (Found: M^+, 173.1210. Calc. for $C_{12}H_{15}N$: *M*, 173.1205); *m*/*z* 173 (100%), 145 (15, *M* − CH_2=CH_2), and 144 (50, *M* − CH_3CH_2).

2,3-*Dihydro*-2-*oxo*-3-*phenylindole* (**26b**) *from* 2-*Aminodiphenylmethanol* (**12b**).—A solution of 2-aminodiphenylmethanol (**12b**) (0.143 g, 0.72 mmol) in 99% formic acid (2 ml, 53 mmol) was added to 98% sulphuric acid (15 ml, 0.28 mmol) at 5 °C during 5 min, and the mixture was kept for 45 min and then poured onto ice. Aqueous work-up with ethyl acetate gave 2,3-dihydro-2-oxo-3-phenylindole (**26b**) (0.102 g, 68%) as prisms, m.p. 185—187 °C (from EtOH), identical (m.p., mixed m.p., i.r., and ^1H n.m.r.) with an authentic sample.[29]

Diphenylacetonitrile (**15**).—98% Sulphuric acid (3 ml, 56 mmol) was added to a solution of diphenylmethanol (**13**) (1.00 g, 5.4 mmol) and potassium cyanide (0.75 g, 11.5 mmol) in TFA (10 ml) at 5 °C and the mixture was kept at room temperature for 6 h. Aqueous work-up with ethyl acetate gave diphenylacetonitrile (**15**) (0.752 g, 71%) as needles, m.p. 67—70 °C (from propan-2-ol), R_F (33% ethyl acetate–toluene) 0.79; $\nu_{max.}$(Nujol) 2 250 cm^{-1}, identical (m.p., mixed m.p., i.r., and ^1H n.m.r.) with an authentic sample.[30]

Treatment of 1-(2-*Aminophenyl*)*cyclohexan*-1-*ol* (**12d**) *with Hydrogen Cyanide in TFA*.—98% Sulphuric acid (0.46 ml, 8.5 mmol) was added dropwise to a solution of the amino alcohol (**12d**) (0.151 g, 0.79 mmol) and potassium cyanide (0.111 g, 1.7 mmol) in TFA (1.5 ml) at 5 °C and the mixture was kept at room temperature for 90 min. Work-up gave 2-(*cyclohex*-1-*enyl*)-*aniline* (**16**) (0.087 g, 64%), identical (t.l.c., ^1H n.m.r.) with the sample prepared earlier.

Treatment of 1-(2-*Aminophenyl*)*cyclohexan*-1-*ol* (**12d**) *with Hydrogen Cyanide in Acetic Acid*.—A solution of the amino alcohol (**12d**) (0.132 g, 0.69 mmol) and potassium cyanide (0.086 g, 1.32 mmol) in glacial acetic acid (10 ml) was refluxed under nitrogen for 90 min. Aqueous work-up and preparative layer chromatography (p.l.c.) [SiO_2; ethyl acetate–toluene (1:2)] gave 2-*methylspiro*[4H-3,1-*benzoxazine*-4,1′-*cyclohexane*] (**19**) (0.060 g, 40%) as an oil, R_F [EtOAc–toluene (1:2)] 0.48; $\nu_{max.}$(neat) 1 640 and 1 600 cm^{-1}; $\delta_H(CDCl_3)$ 7.30—6.90 (4 H, m, ArH), 2.17 (3 H, s, Me), and 2.00—1.50 (10 H, m, 5 × CH_2) (Found: M^+, 215.1302. $C_{14}H_{17}NO$ requires *M*, 215.1310); *m*/*z* 215 (25%) and 172 (100, *M* − CH_3CO), and 2′-(*cyclohex*-1-*enyl*)*acetanilide* (**18**) (0.038 g, 25%) as needles, m.p. 82—82.5 °C (from light petroleum) (Found: C, 78.4; H, 7.7; N, 6.4 $C_{14}H_{17}NO$ requires C, 78.1; H, 7.9; N, 6.5%), R_F [EtOAc–toluene (1:2)] 0.33; $\nu_{max.}$(Nujol) 3 250, 3 040, 1 670, and 1 520 cm^{-1}; $\delta_H(CDCl_3)$ 8.25 (1 H, br s, *J* 7 Hz, *o*-ArH), 7.42 (1 H, br m, NH) 7.35—6.95 (3 H, m, ArH), 5.80 (1 H, br m, =CH), 2.25 (4 H, br m, CH_2C=CCH_2), 2.20 (3 H, s, Ac), and 1.80 (4 H, br m, 2 × CH_2); *m*/*z* 215 (25%, M^+) and 172 (100, *M* − CH_3CO).

Treatment of 2-(2-*Aminophenyl*)*adamantan*-2-*ol* (**12f**) *with Hydrogen Cyanide in TFA*.—The amino alcohol (**12f**) (0.105 g, 0.43 mmol) was added to a solution of potassium cyanide (0.138 g, 2.12 mmol) in TFA (5 ml) at 5 °C and the mixture was kept at room temperature for 2 h, after which the initial crimson colour had completely faded. Aqueous work-up with diethyl ether and chromatography (p.l.c.; SiO_2; toluene) gave 2-(2-*trifluoroacetamidophenyl*)*adamantan*-2-*ol* (**20**) (0.040 g, 27%) as needles, m.p. 139.5—140.5 °C (from light petroleum); R_F (toluene) 0.75; $\nu_{max.}$(Nujol) 3 430, 3 240, 1 700, 1 530, and 1 160 cm^{-1}; $\delta_H(CDCl_3)$ 10.5 (1 H, br m, NH), 8.15 (1 H, dd, *J* 6 and 2 Hz, *o*-ArH), 7.50 (1 H, dd, *J* 8 and 2 Hz, *o*-ArH), 7.40—7.00 (2 H, m, ArH), 2.60—2.30 (4 H, br m, adamantyl H), and 2.00—1.55 (10 H, br m, adamantyl H) (Found: M^+, 339.1445. $C_{18}H_{20}F_3NO_2$ requires *M*, 339.1447); *m*/*z* 339 (80%) and 321 (100, *M* − H_2O).

Spiro[4H-3,1-*benzoxazine*-4,1′-*cyclohexane*] (**21**).—98% Sulphuric acid (1 ml) and glacial acetic acid (1 ml) were added to a mixture of the formamido alcohol (**11d**) (0.063 g, 0.29 mmol) and potassium cyanide (0.026 g, 0.4 mmol) in glacial acetic acid (5 ml) at 5 °C, and the mixture was kept at room temperature for 16 h. Aqueous work-up gave the unstable *benzoxazine* (**21**), R_F (10% MeOH–$CHCl_3$) 0.65; $\nu_{max.}$(neat) 1 620 cm^{-1}; $\delta_H(CDCl_3)$ 7.15 (5 H, s, ArH and N=CH), and 1.75 (10 H, br m, 5 × CH_2) (Found: M^+, 201.1158. $C_{13}H_{15}NO$ requires *M*, 201.1154); *m*/*z* 201 (40%) and 158 (100, *M* − HNCO). A similar reaction with sulphuric acid (3 ml) and potassium cyanide (0.1 g) in methanol (2 ml) at room temperature for 1 h gave the anilinocyclohexene (**16**) (90%), identical with the earlier samples.

2-(2-*Aminophenyl*)-2-*cyanoadamantane* (**24f**).—2-(2-Formamidophenyl)adamantan-2-ol (**11f**) (1.40 g, 5.17 mmol) and sodium cyanide (0.537 g, 10.96 mmol) were kept in dry DMF (25 ml) under nitrogen at 80 °C for 120 h. The mixture was poured into water (100 ml) and extracted with ethyl acetate (3 × 50 ml). The extracts were washed successively with water (50 ml) and brine (50 ml), dried ($MgSO_4$), and evaporated to give the *amino nitrile* (**24f**) (1.303 g, 100%), which was used directly in the next step. A sample was crystallised as cubes, m.p. 186—187.5 °C (from methanol), R_F (10% MeOH—$CHCl_3$) 0.88; $\nu_{max.}$(Nujol) 3 430, 3 350, 2 225, and 1 640 cm^{-1}; $\delta_H(CDCl_3)$ 7.35—6.65 (4 H, m, ArH), 3.65 (2 H, br m, NH_2), 3.05 (2 H, br m, 2 × bridgehead H), 2.50 (2 H, br d, *J* 13.5 Hz, 2 × CH_AH_B), and 2.10—1.50 (10 H, br m, 4 × CH and 3 × CH_2) (Found: M^+, 252.1621. $C_{17}H_{20}N_2$ requires *M*, 252.1627); *m*/*z* 252 (100%) and 209 (10, *M* − $HNCNH_2$).

2′-*Aminospiro*[*adamantane*-2,3′-3′H-*indole*] (**25f**).—The formamido alcohol (**11f**) (0.138 g, 0.51 mmol) and dry tetrabutylammonium cyanide (0.672 g, 2.56 mmol) were heated at 80 °C in dry DMF (3 ml) under nitrogen for 160 h. Aqueous work-up gave the *amino*-3H-*indole* (**25f**) (0.55 g, 43%) as needles, m.p. 261—262 °C (decomp.) (from EtOAc), R_F (10% MeOH–$CHCl_3$) 0.08; $\nu_{max.}$(Nujol) 3 480, 3 320, 1 640, and 1 540 cm^{-1}; δ_H [$(CD_3)_2SO$] 7.85 (1 H, d, *J* 6 Hz, *o*-ArH), 7.15—6.75 (3

H, m, ArH), 3.70 (2 H, br m, NH_2), 2.85 (2 H, d, *J* 15 Hz, 2 × CH_AH_B), 2.75 (2 H, br m, 2 × bridgehead H), and 2.15—1.20 (10 H, br m, 4 × CH and 3 × CH_2) (Found: M^+, 252.1654. $C_{17}H_{20}N_2$ requires *M*, 252.1627); *m/z* 252 (100%).

*The Amino-*3H-*indoles* (**25c—e**).—Typically, the formamidobenzyl alcohols (**11c—e**) (1.7 mmol) and sodium cyanide (3.39 mmol) were heated at 80 °C in dry DMF (10 ml) under nitrogen for the time stated. The mixture was poured into water (40 ml) and worked up to give crude product, which was triturated with ether. The following aminoindolenines were obtained crystalline. 2-*Amino*-3,3-*diphenyl*-3H-*indolenine* (**25c**) (28 h; 88%), as needles, m.p. 255—255.5 °C (from toluene), R_F (10% MeOH–$CHCl_3$) 0.21; $\nu_{max.}$(Nujol) 3 450, 3 300, 1 680, 1 660, and 1 560 cm^{-1}; δ_H($CDCl_3$) 7.30 (10 H, s, 2 × Ph) 7.30—6.80 (4 H, m, ArH), and 5.60 (2 H, s, NH_2) (Found: M^+, 284.1288. $C_{20}H_{16}N_2$ requires *M*, 284.1314); *m/z* 284 (100%), 207 (20, *M* − Ph), and 180 (55, 207 − HCN).

2′-*Amino*[*spirocyclohexane*-1,3′-3′H-*indole*] (**25d**) (48 h; 8%), needles, m.p. 241—242 °C (from toluene–light petroleum) R_F (10% MeOH–$CHCl_3$) 0.07; $\nu_{max.}$(Nujol) 3 330, 3 175, 1 690, 1 645, and 1 555 cm^{-1}; δ_H($CDCl_3$) 7.45 (1 H, d, *J* 7 Hz, *o*-ArH), 7.30 (2 H, d, *J* 6 Hz, ArH), 7.10—6.90 (1 H, m, ArH), 3.97 (2 H, br d, NH_2), and 2.00—1.50 (10 H, m, 5 × CH_2) (Found: M^+, 200.1314. $C_{13}H_{16}N_2$ requires *M*, 200.1314); *m/z* 200 (100%) and 145 (65, M − C_4H_7).

2-*Aminospiro*[3H-*indole*-3,2′-*norbornane*] (**25e**) 58 h (12% + 32% by subsequent chromatography), needles, m.p. 191—194 °C (from toluene) (Found: C, 79.5; H, 7.85; N, 13.0. $C_{14}H_{16}N_2$ requires C, 79.2; H, 7.6; N, 13.2%); R_F (10% MeOH–$CHCl_3$) 0.12; $\nu_{max.}$(Nujol) 3 450 and 3 300, 1 660, 1 640, and 1 540 cm^{-1}; δ_H($CDCl_3$) 7.16—7.00 (4 H, m, ArH), 5.60 (2 H, br m, NH_2), 2.50 (1 H, s, bridgehead H), 2.25 (1 H, s, bridgehead H), and 2.24—1.52 (8 H, br m, 4 × CH_2) (Found: M^+, 212.1310. $C_{14}H_{16}N_2$ requires 212.1313); *m/z* 212 (40%) and 145 (100, *M* − C_5H_7). In each case, these compounds crystallised with varying amounts of water of crystallisation, which made combustion analysis unreliable. In the case of compounds (**25d**) and **e**), the ethereal mother liquors contained the elimination products (**16**) [from (**25d**) (80%) already characterised] and, from the spiro norbornane (**25e**), 2-(2-*aminophenyl*)*norborn*-2-*ene* (35%) as an oil, R_F (50% diethyl ether–light petroleum) 0.71; $\nu_{max.}$(neat) 3 450, 3 350, and 1 620 cm^{-1}; δ_H($CDCl_3$) 7.20—6.45 (4 H, m, ArH), 6.15 (1 H, d, *J* 3 Hz, =CH), 3.80 (2 H, br m, NH_2), 3.20 (1 H, br m, bridgehead H), 3.00 (1 H, br m, bridgehead H), and 1.95—1.05 (6 H, m, 3 × CH_2) (Found: M^+, 185.1206. $C_{13}H_{15}N$ requires *M*, 185.1204); *m/z* 185 (60%), 157 (100, *M* − C_2H_4), and 130 (45, 157 − HCN).

*Hydrolysis of the Amino-*3H-*indoles* (**25**) *to give Oxindoles* (**26**).—Hydrogen chloride gas was passed through a solution of the amino-3*H*-indoles (**25c—f**) (0.89 mmol) in chloroform (20 ml) at room temperature for 10 min, and the solvent was then evaporated off under reduced pressure. The crude hydrochloride was heated in water (35 ml) in a sealed tube at 165 °C for 6 days. The crude product was collected by filtration and recrystallised to give the oxindole. The following oxindoles were prepared this way. 3,3-Diphenyloxindole (**26c**) (91%), needles, m.p. 227—228.5 °C (from ethanol), identical (m.p., mixed m.p., i.r., and ^1H n.m.r.) with authentic material.[15]

Spiro[cyclohexane-1,3′-3′*H*-indol]-2′(1′*H*)-one (**26d**) (87%), prisms, m.p. 121—123 °C (from light petroleum), identical (m.p., mixed m.p., i.r., and ^1H n.m.r.) with authentic material.[16]

Spiro[3H-*indole*-3,2′-*norbornan*]-2(1H)-*one* (**26e**) (the Wallace oxindole) (94%), needles, m.p. 173.5—174.5 °C (from chloroform–light petroleum, and sublimation) (Found: C, 78.9; H, 7.2; N, 6.4. $C_{14}H_{15}NO$ requires C, 78.8; H, 7.1; N, 6.6%); R_F (10% MeOH–$CHCl_3$) 0.5; $\nu_{max.}$($CHCl_3$) 3 425, 3 180br, 1 700, and 1 620 cm^{-1}; $\nu_{max.}$(Nujol) 3 400, 3 150, 1 700, and 1 610 cm^{-1}; δ_H ($CDCl_3$; 400 MHz) 7.501 (1 H, br s, N-H), 7.190 (1 H, t, *J* 8 Hz, oxindole 6-H), 7.163 (1 H, d, *J* 7.5 Hz, oxindole 4-H), 7.026 (1 H, t, *J* 7.5 Hz, oxindole 5-H), 6.855 (1 H, d, *J* 8 Hz, oxindole 7-H), 2.600 (1 H, d, *J* 10 Hz, H^a), 2.472 (1 H, br s, 1-H), 2.296 (1 H, s, 4-H), 2.193 (1 H, dt, *J* 12 and 1 Hz, 3-H_{exo}), 1.89 (1 H, m, 6-H_{endo}), 1.80 (1 H, m, 5-H_{exo}), 1.48 (3 H, m, 3-H_{endo}, 5-H_{endo}, and 6-H_{exo}), and 1.413 (1 H, d, *J* 10 Hz, H^b); δ_C($CDCl_3$) 141.3 (s), 133.2 (s), 127.3 (d), 124.9 (d), 121.5 (d), 109.5 (d), 54.3 (s), 47.7 (d), 41.2 (t), 38.0 (t), 37.1 (d), 28.5 (t), and 26.5 p.p.m. (t); *m/z* 213 (35%, M^+) and 146 (100, *M* − C_5H_7).

Spiro[*adamantane*-2,3′-3′H-*indol*]-2′(1′H)-*one* (**26f**).—This was prepared in the same way, but starting from nitrite (**24f**) to give the *title oxindole* (93%) as spars, m.p. 245—247 °C (from toluene–light petroleum) (Found: C, 80.8; H, 7.35; N, 5.5%; M^+, 253.1468. $C_{17}H_{19}NO$ requires C, 80.6; H, 7.55; N, 5.5%; *M*, 253.1467); R_F (33% EtOAc–toluene) 0.67; $\nu_{max.}$($CHCl_3$) 3 450, 3 200, 1 700, and 1 610 cm^{-1}; δ_H($CDCl_3$) 7.75 (1 H, br m, NH), 7.60 (1 H, d, *J* 7 Hz, *o*-ArH), 7.30—6.65 (3 H, m, ArH), 3.05 (2 H, br d, *J* 12 Hz, CH_2), 2.60 (2 H, br d, *J* 15 Hz, CH_2), and 2.00—1.20 (10 H, br m, adamantyl H); *m/z* 253 (5%), 85 (65), and 83 (100).

(*o-Fluorobenzyl*)*triphenylphosphonium Chloride*.—*o*-Fluorobenzyl chloride (8.8 ml, 69 mmol) and triphenylphosphine (20 g, 74 mmol) were refluxed in dry toluene (30 ml) for 16 h, and the mixture was then cooled and filtered. The solid residue was washed with cold dry diethyl ether (2 × 30 ml) and dried *in vacuo* to give the phosphonium salt (26.6 g, 88%) as rhombic prisms, m.p. 298—300 °C; δ_H[$(CD_3)_2SO$] 7.80—7.68 (15 H, m, 3 × Ph), 7.10 (4 H, m, ArH), and 5.35 (2 H, d, *J* 16 Hz, PhCH_2).

o-Fluorophenyl(*cyclohexylidene*)*methane*.—A solution of sodium ethoxide (70 mmol) in dry ethanol (50 ml) was slowly added to a stirred solution of the above phosphonium salt (24.8 g, 60 mmol) in dry ethanol (50 ml) at 20 °C; this caused the formation of both a bright orange colour and a precipitate. After 10 min, a solution of cyclohexanone (5.96 g, 60 mmol) in ethanol (15 ml) was added and the mixture was refluxed until the orange colour had disappeared completely (30 min). The ethanol was evaporated off, water (50 ml) was added, and the suspension was filtered. The solid and the aqueous phase were extracted with pentane (5 × 50 ml), and the extract was washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure, and the residue distilled to give the *title fluoro olefin* 7.48 g, 66%) as an oil, b.p. 66—67 °C/0.07 mmHg; $\nu_{max.}$(neat) 3 050, 1 650, 1 610, 1 580, 1 220, and 750 cm^{-1}; δ_H(CCl_4) 7.20—6.60 (4 H, m, ArH), 6.00 (1 H, s, PhC*H*=), 2.25 (4 H, br m, 2 × allylic CH_2), and 1.63 (6 H, br m, 3 × CH_2) (Found: M^+, 190.1155. $C_{13}H_{15}F$ requires *M*, 190.1157); *m/z* 190 (65%) and 81 (100, C_6H_9).

2-(o-*Fluorophenyl*)-1-*oxaspiro*[2.5]*octane* (**29**).—A solution of *m*-chloroperbenzoic acid (MCPBA) (3.34 g, 16.5 mmol) in dry, ethanol-free chloroform (25 ml) was added dropwise to a stirred solution of the aforementioned fluoro olefin (2.10 g, 11 mmol) in chloroform (20 ml) and stirred for 3.5 h at 0 °C. After filtration, the solution was washed successively with 10% aqueous sodium sulphite (2 × 25 ml), saturated aqueous sodium hydrogen carbonate (2 × 25 ml), and brine, dried (Na_2CO_3), and distilled to give the *fluorophenyl epoxide* (**29**) (2.02 g, 89%), b.p. 91—92 °C/0.15 mmHg; $\nu_{max.}$(neat) 1 235 and 760 cm^{-1}; δ_H(CCl_4) 7.35—6.55 (4 H, m, ArH), 3.70 (1 H, s, 2-H), and 2.00—1.00 (10 H, m, 5 × CH_2) (Found: M^+, 206.1107. $C_{13}H_{15}FO$ requires *M*, 206.1107); *m/z* 206 (6%) and 105 [100, *M* − H_2O and C_6H_{11})].

Details of the various conditions under which the products

(**30**)—(**34**) were produced can be found in the Ph.D. Thesis of I. H. M. W. (Cambridge, 1980).

Treatment of the Fluorophenyl Epoxide with Aluminium Trichloride.—A solution of fluorophenyl epoxide (4.6 g, 22 mmol) in methylene dichloride (10 ml) was added to a stirred suspension of aluminium chloride (2.97 g, 22 mmol) in methylene dichloride (60 ml) at 5 °C. After 3 min, water was added to the red-brown solution, causing the colour to fade rapidly, and the organic layer was separated, washed successively with saturated aqueous sodium hydrogen carbonate (2 × 30 ml) and brine (30 ml), dried (Na_2CO_3), and evaporated to give a mixture (4.186 g, 91% of the aldehyde (**35**) and ketone (**36**) in the ratio 72:28 (^{1}H n.m.r.). This mixture was used directly in the next step. Characteristic signals for each component were present at $\nu_{max.}$(neat) 1 725 (CHO) and 1 690 (ArCO) cm^{-1}, and $\delta_H(CDCl_3)$ 9.56 (d, *J* 4 Hz, CHO) and 2.25 (m, ArCOC*H*).

1-(o-*Fluorophenyl*)*cyclohexane*-1-*carboxylic Acid* (**39**).—Sulphuric acid (3.5 ml; 98%) and chromium trioxide (4 g) in water[31] (12 ml) were added dropwise to the stirred mixture (4.186 g) of the aldehyde (**35**) and ketone (**36**) in acetone (75 ml) at 5 °C, and the mixture was stirred at 20 °C for 4 h. Aqueous work-up with diethyl ether, and an aqueous sodium carbonate wash, gave, in the ethereal layer, *cyclohexyl o-fluorophenyl ketone* (**36**) (0.578 g, 12% recovery), $\nu_{max.}$(neat) 1 690, 1 610, and 1 580 cm^{-1}; $\delta_H(CDCl_3)$ 7.84—7.02 (4 H, m, ArH), 3.15 (1 H, m, ArCOC*H*), 2.05—1.64 (4 H, m, CH_2CHRCH_2), and 1.63—1.12 [6 H, m, $(CH_2)_3$] (Found: M^+, 206.1097. $C_{13}H_{15}FO$ requires *M*, 206.1098); *m/z* 206 (20%), 151 (25, $M - C_4H_7^+$), 138 (15, $M - C_5H_8$), and 123 (100, C_7H_4FO). The aqueous carbonate layer was acidified (35% HCl) and extracted with diethyl ether (4 × 30 ml) to give after work-up, the *fluoro acid* (**39**) [2.464 g, 50% based on (**29**)] as needles, m.p. 124—125 °C (from light petroleum) (Found: 70.3; H, 6.7. $C_{13}H_{15}FO_2$ requires C, 70.3; H, 6.75%), $\nu_{max.}$(Nujol) 2 700 and 1 700 cm^{-1}; $\delta_H(CDCl_3)$ 11.23 (1 H, m, CO_2H), 7.50—6.70 (4 H, m, ArH), and 2.60—1.30 (10 H, m, 5 × CH_2) (Found: M^+, 222.1054. $C_{13}H_{15}FO_2$ requires *M*, 222.1056); *m/z* 222 (20%), 177 (70, $M - CO_2H$), and 110 (100, $C_7H_7F^+$).

1-[o-*Fluoro*-α-(*trimethylsilylmethyl*)*benzyl*]*cyclohexan*-1-*ol* (**37**).—Trimethylsilylmethylmagnesium chloride[32] (17.4 mmol), prepared from trimethylsilylmethyl chloride and magnesium in dry THF (10 ml), was added to anhydrous copper(I) chloride (2.4 mmol) at −10 °C under nitrogen. The mixture was stirred at −10 °C for 10 min, then a solution of the epoxide (**29**) (0.895 g, 4.34 mmol) in dry THF (10 ml) was added and the mixture was stirred at 35 °C for 22 h. Water (30 ml) was added cautiously to the cooled mixture and the resulting slurry was extracted with diethyl ether (6 × 5 ml). The emulsified organic phase was shaken with sodium chloride (15 g), then decanted, dried ($MgSO_4$), and evaporated under reduced pressure, and the residue was chromatographed (SiO_2, short column), with methylene dichloride as eluant, to give the γ-*silyl alcohol* (**37**) (0.838 g, 72%) as a viscous oil, $R_F(CH_2Cl_2)$ 0.5; $\nu_{max.}$(neat) 3 475, 1 585, and 1 250 cm^{-1}; $\delta_H(CCl_4)$ 7.70—6,80 (4 H, m, ArH), 3.15 (1 H, t, *J* 8 Hz, ArC*H*), 2.10—0.90 (11 H, m, 5 × CH_2 and OH), 1.11 (2 H, dd, *J* 8 and 4 Hz, CH_2Si), and −0.22 (9 H, s, $SiMe_3$) (Found: $M^+ - H_2O$, 276.1715. $C_{17}H_{25}FSi$ requires *m/z*, 276.1710); *m/z* no M^+, 276 (6, $M - H_2O$), 196 (90, $M - C_6H_{10}O$), and 104 (100).

1-*Fluoro*-2-(1-*vinylcyclohexyl*)*benzene* (**38**).—The silyl alcohol (**37**) (0.372 g, 1.27 mmol) was kept in TFA (0.5 ml) at 20 °C for 2 h. Aqueous work-up gave the *olefin* (**38**) (0.228 g, 88%), R_F (light petroleum) 0.44; $\nu_{max.}$(neat) 3 070, 1 635, 1 610, 1 580, 1 220, and 910 cm^{-1}; $\delta_H(CCl_4)$ 7.50—6.65 (4 H, m, ArH), 5.95 (1 H, ddd, *J* 2, 11, and 17 Hz, C*H*=CH_2), 4.97 (1 H, ddd, *J* 1, 2, and 11 Hz, *cis*-CH=C*H*H), 4.77 (1 H, ddd, *J* 1, 2, and 17 Hz, *trans*-CH=CH*H*), 2.00 (4 H, m, $CH_2CRR'CH_2$), and 1.55 (6 H, m, $[CH_2]_3$) (Found: M^+, 204.1313. $C_{14}H_{17}F$ requires *M*, 204.1314); *m/z* 204 (35%), 123 (20, $C_8H_8F^+$), and 122 (100, $C_8H_7F^+$).

Ozonolysis of 1-*Fluoro*-2-(1-*vinylcyclohexyl*)*benzene* (**38**).—Ozonised oxygen was passed through a solution of the olefin (**38**) (0.228 g, 1.1 mmol) in ethyl acetate (10 ml) at 0 °C for 3 h. The solvent was evaporated off under reduced pressure, and the residue was dissolved in acetone (20 ml). Jones' reagent[31] was added to this solution at 0 °C dropwise until a permanent brown colour was observed. Aqueous work-up for acid products (0.114 g) and chromatography (SiO_2, p.l.c.) gave the acid (**39**) (0.056 g, 22%) as needles, m.p. 120—122 °C.

1-(o-*Fluorophenyl*)*cyclohexane*-1-*carboxamide* (**40a**).—Freshly distilled thionyl chloride (0.342 ml, 4.7 mmol) and the fluoroacid (**39**) (0.520 g, 2.34 mmol) were heated at 50 °C in dry chloroform (10 ml) for 24 h. Dry ammonia was then passed through the solution at 5 °C for 20 min, then water (10 ml) and chloroform (10 ml) were added. The organic layer was separated, washed successively with saturated aqueous sodium hydrogen carbonate (5 ml) and brine (5 ml), dried ($MgSO_4$), and evaporated to give the *amide* (**40a**) (0.432 g, 83%) as rectangular plates, m.p. 89—89.5 °C (from chloroform–light petroleum) (Found: C, 70.4; H, 7.2; N, 6.4. $C_{13}H_{16}FNO$ requires C, 70.6; H, 7.24; N, 6.3%); $\nu_{max.}$(Nujol) 3 480, 3 350, 3 280, 3 140, 1 680, and 1 220 cm^{-1}; $\delta_H(CDCl_3)$ 7.60—6.69 (4 H, m, ArH), 5.95 (1 H, m, NH), 5.35 (1 H, m, NH), 2.09 (4 H, m, $CH_2CR_2CH_2$), and 1.49 (6 H, m, $[CH_2]_3$).

Synthesis of 1-(2-*Halogenophenyl*)*cyclohexane*-1-*carboxamides* (**40**).—An *o*-halogenophenylacetonitrile (**41**) (15 mmol) and powdered potassium hydroxide (40 mmol) were stirred in dry dimethyl sulphoxide (25 ml) at room temperature for 5 min, after which pentamethylene dibromide (16 mmol) was added. The mixture was stirred at room temperature for 24 h, and then at 90—100 °C for 1.5 h. The cooled solution was diluted with dil. hydrochloric acid solution (400 ml; 2M) and extracted with methylene dichloride (3 × 50 ml). The combined extracts were dried ($MgSO_4$) and evaporated, and the residue was chromatographed on silica gel with hexane–diethyl ether mixtures as eluant. In all cases the only identifiable product obtained was the desired title compound, which was further purified by distillation or recrystallisation as appropriate. The following compounds were thus prepared. 1-(2-*Fluorophenyl*)*cyclohexane*-1-*carbonitrile* (48%) b.p. 130—135 °C/2—3 mmHg, $\nu_{max.}$ (liquid film) 2 240 and 760 cm^{-1}; $\delta_H(CDCl_3)$ 6.9—7.7 (4 H, m) and 1.1—2.7 (10 H, m) (Found: M^+, 203.110 87. $C_{13}H_{14}FN$ requires *M*, 203.111 03); *m/z* 203 (43%, *M*), 158 (57), 157 (100), 131 (15), 121 (27), and 120 (19).

1-(2-*Chlorophenyl*)*cyclohexane*-1-*carbonitrile* (27%) as prisms, m.p. 97.5—98.5 °C (from hexane–acetone) (Found: C, 71.1; H, 6.65; N, 6.4. $C_{13}H_{14}ClN$ requires C, 71.1; H, 6.4; N, 6.4%); $\nu_{max.}$(KBr) 2 215 and 750 cm^{-1}; $\delta_H(CDCl_3)$ 7.7—7.3 (4 H, m), 2.8—2.3 (2 H, m), and 2.1—1.2 (8 H, m); *m/z* 219/221 (68/23%, M^+), 184 (19, M − Cl), 165 (47), 164 (71), 163 (100), 128 (82), and 115 (39).

1-(2-*Bromophenyl*)*cyclohexane*-1-*carbonitrile* (22%) as prisms, m.p. 101—101.5 °C (from acetone) (Found: C, 59.2; H, 5.35; N, 5.5. $C_{13}H_{14}BrN$ requires C, 59.1; H, 5.3; N, 5.3%); $\nu_{max.}$(KBr) 2 240, and 770 cm^{-1}; $\delta_H(CDCl_3)$ 7.8—7.0 (4 H, m), 2.7—2.1 (2 H, m), and 2.1—1.1 (8 H, m); *m/z* 263/265 (55%, M^+), 208/210 (50), 207/209 (100), 182 (43), 129 (43), 128 (100), and 115 (52).

Synthesis of 1-(2-*Halogenophenyl*)*cyclohexane*-1-*carboxamides* (**40**).—A 1-(2-halogenophenyl)cyclohexane-1-carbonitrile (2.5 mmol) was kept at 50 °C in a mixture of glacial acetic acid (4 ml) and conc. sulphuric acid (4 ml) for 40—45 h. After being cooled and then carefully neutralised with cold aqueous sodium hydroxide solution, the resulting mixture was extracted with methylene dichloride (3 × 20 ml). The combined extracts were dried ($MgSO_4$), filtered, and evaporated. Chromatography on silica gel with hexane–acetone mixtures gave starting material (<5%) followed by the amides. The following amides were prepared. 1-(2-Fluorophenyl)cyclohexane-1-carboxamide (**40a**) (74%), m.p. 88—92 °C (from acetone), identical with the sample prepared earlier.

1-(2-*Chlorophenyl*)*cyclohexane*-1-*carboxamide* (**40b**) as prisms (87%), m.p. 105—106 °C (from acetone, then hexane) (Found: C, 65.2; H, 7.1; N, 6.0. $C_{13}H_{16}ClNO$ requires C, 65.7; H, 6.8; N, 5.9%); $\nu_{max.}$(KBr) 3 485, 3 350, 3 180, 1 675, 1 662, and 760 cm^{-1}; δ_H($CDCl_3$) 7.7—7.3 (4 H, m), 6.0—4.7 (2 H, br s, NH_2), 2.65—2.0 (4 H, m), and 2.0—1.0 (6 H, m); *m/z* 237 (10%, M^+), 203 (17), 202 (100, M − Cl), 193 (19, M − $CONH_2$), 127 (29), and 125 (81, chlorotropylium ion).

1-(2-*Bromophenyl*)*cyclohexane*-1-*carboxamide* (**40c**) (68%) as prisms, m.p. 107.5—108 °C (from acetone) (Found: C, 55.2; H, 5.4; N, 5.3. $C_{13}H_{16}BrNO$ requires C, 55.3; H, 5.7; N, 5.0%; $\nu_{max.}$(KBr) 3 475, 3 360, 3 195, 1 660, and 757 cm^{-1}; δ_H($CDCl_3$) 7.8—6.95 (4 H, m), 6.0—4.7 (2 H, br s, NH_2), 2.5—2.0 (4 H, m), and 2.0—1.2 (6 H, m); *m/z* 281/283 (2%, M), 237/239 (10, M − $CONH_2$), 203 (21), 202 (100, M − Br), and 169/171 (55/51, bromotropylium ion).

Spiro[*cyclohexane*-1,3′-3′H-*indol*]-2′(1′H)-*one* (**2d**).—A solution of a 1-(2-halogenophenyl)cyclohexane-1-carboxamide (**40**) (1 mmol) in dry DMF (4 ml) was stirred with lithium hydride (40 mg, 5 mmol) at 135—140 °C under nitrogen for 2—2.5 h. The DMF was removed under reduced pressure and the residue was partitioned between dil. hydrochloric acid (20 ml; 2M) and methylene dichloride (3 × 8 ml). The organic phases were dried ($MgSO_4$) and evaporated, and the product was chromatographed (SiO_2; hexane–acetone). The oxindole (**26d**) was obtained as prisms, m.p. 123—124 °C (from hexane–ethyl acetate, or from acetone) (lit.,[16] 124 °C) in yields of 77, 64, and 82.5% respectively from the fluoro, chloro, and bromo precursors. In the case of the chloro compound, starting material (17%) was also recovered from the column.

2-(2-*Fluorobenzylidene*)*bicyclo*[2.2.1]*heptane*.—A solution of sodium ethoxide (20 mmol) in dry ethanol (50 ml) was added dropwise to a stirred solution of *o*-fluorobenzyl(triphenyl)-phosphonium chloride (24.8 g) in dry ethanol (50 ml) under nitrogen at 20 °C. After 10 min, a solution of bicyclo-[2.2.1]heptan-2-one (6.6 g) in dry ethanol (25 ml) was added, and the mixture was refluxed until the orange colour had faded (2 h), cooled, filtered, and evaporated, and the residue was chromatographed on silica gel (100 g) with hexane–ethyl acetate (8:2) as eluant to give a mixture of the *Z*- and *E*-fluoro olefin (9.84 g, 81%), b.p. 97—99 °C/0.6 mmHg; $\nu_{max.}$(CCl_4) 3 050, 1 660, and 1 230 cm^{-1}; δ_H(CCl_4) 7.5—6.6 (4 H, m, ArH), 6.4 (0.5 H, s, ArC*H*= *Z* or *E*), 6.1 (0.5 H, s, ArC*H*= *E* or *Z*), 3.1 (0.5 H, s, C=CCH at bridgehead, *Z* or *E*), 2.85 (0.5 H, s, C=CCH at bridgehead, *E* or *Z*), and 2.6—1.1 (9 H, m, CH and 4 × CH_2) (Found: M^+, 202.1157, $C_{14}H_{15}F$ requires M, 202.1157); *m/z* 202 (71%, M^+) and 79 (100).

3-(2-*Fluorophenyl*)*spiro*[*oxirane*-2,2′-*norbornane*](**42**).—A solution of MCPBA (13.85 g) in dry, ethanol-free chloroform (105 ml) was added dropwise to a stirred solution of the previously prepared fluoro olefin (9.21 g) in dry chloroform (83 ml) at 0 °C, and the mixture was then stirred for 3 h at 0 °C. Work-up as in the preparation of compound (**29**) gave the *epoxide* (**42**) (8.83 g, 88%), b.p. 80—82 °C/0.4 mmHg; $\nu_{max.}$(CCl_4) 2 960 and 1 230 cm^{-1}; δ_H(CCl_4) 7.40—6.75 (4 H, m, ArH), 3.95 (1 H, m, ArC*H*), 2.35 (1 H, m, bridgehead CH), and 2.2—0.95 (9 H, m, CH and 4 × CH_2) (Found: M^+, 218.1107. $C_{14}H_{15}FO$ requires M, 218.1114); *m/z* 218 (54%, M^+) and 79 (100).

2-(2-*Fluorophenyl*)*bicyclo*[2.2.1]*heptane*-2-*carboxylic Acid* (**46**).—TFA (27 ml) was added dropwise to a stirred solution of the epoxide (**42**) (7.2 g) in dry methylene dichloride (90 ml) at 20 °C. After 15 min, water (120 ml) was added, and the organic layer was separated, washed successively with saturated aqueous sodium hydrogen carbonate and brine, dried (Na_2SO_4), and evaporated to give a mixture of aldehydes (**44**) and (**45**) and ketones (**43**) (7.0 g, 97%). This mixture (6 g) was oxidised, in the same way as described in the preparation of the acid (**39**), to give the mixture of ketones (**43**) (3.36 g, 56%), $\nu_{max.}$(CCl_4) 1 675 and 1 600 cm^{-1}; δ_H(CCl_4) 7.95—7.6 (1 H, m, ArH), 7.55—6.75 (3 H, m, ArH), 3.75—2.9 (1 H, m, CHCO), and 2.7—1.0 (10 H, m, 2 × CH and 4 × CH_2), and the *fluoro acids* (**46**) and (**47**) (2 g, 40%). The corresponding mixture of methyl esters (CH_2N_2); diethyl ether; 1 h) had δ_H ($CDCl_3$; 400 MHz) 7.6—6.8 (4 H, m, ArH), 3.6 (2.7 H, s, OMe, *endo* ester), 3.56 (0.3 H, s, OMe *exo* ester), 3.2 (0.1 H, br s, bridgehead CH, *exo* ester), and 3.0 (0.9 H, br s, bridgehead CH, *endo* ester).

The mixture of acids was crystallised to give the pure endo *acid* (**46**) (1.8 g, 30%), m.p. 157—158 °C (from aqueous EtOH; $\nu_{max.}$($CHCl_3$) 3 500 and 1 695 cm^{-1}; δ_H($CDCl_3$) 10.2 (1 H, br s, CO_2H), 7.65—6.8 (4 H, m, ArH), 3.05 (1 H, br s, bridgehead CH), 2.65 (1 H, dt, *J* 15 and 1 Hz, 3-H_{exo}), 2.3 (1 H, br s, bridgehead CH), and 2.0—1.0 (7 H, m, CH and 3 × CH_2) (Found: M^+, 234.1056. $C_{14}H_{15}FO_2$ requires M, 234.1056); *m/z* 234 (43% M^+) and 168 (100).

2-(2-*Fluorophenyl*)*bicyclo*[2.2.1]*heptane*-2-*carboxamide*.—A mixture of thionyl chloride (1 ml) and the fluoro acid (**46**) (1.6 g) in dry chloroform (30 ml) was heated at 50 °C for 26 h. Dry ammonia was passed through the solution at 5 °C for 1 h, then water and chloroform were added. The organic layer was separated, washed with saturated brine, dried (Na_2SO_4), and evaporated to give the *amide* (1.4 g, 88%), m.p. 132—133 °C (from $CHCl_3$–hexane); $\nu_{max.}$(KBr) 3 470, 3 270, 3 140, 1 680, and 1 220 cm^{-1}; δ_H($CDCl_3$) 7.7—6.9 (4 H, m, ArH), 5.6 (1 H, br s, NH), 5.15 (1 H, br s, NH), 2.9 (1 H, br s, bridgehead CH), 2.8 (1 H, dt, *J* 14 and 0.9 Hz, 3-H_{exo}), 2.35 (1 H, br s, bridgehead CH), and 1.15—1.9 (7 H, m, CH and 3 × CH_2) (Found: M^+, 223.1216. $C_{14}H_{16}FNO$ requires M, 233.1228); *m/z* 233 (8.9%, M^+) and 109 (100).

Spiro[3H-*indole*-3,2′-*norbornan*]-2(1H)-*one* (**48**) (*The Loreto Oxindole*).—2-*exo*-(2-Fluorophenyl)norbornane-2-*endo*-carboxamide (107 mg, 0.46 mmol) was stirred with lithium hydride (20 mg, 2.5 mmol) in dry DMF (2 ml) under nitrogen at 135—140 °C for 8 h. The solvent was removed under reduced pressure and the residue was dissolved in aqueous hydrochloric acid (20 ml; 2M) and extracted with methylene dichloride (3 × 15 ml). The combined extracts were dried ($MgSO_4$) and evaporated, and the residue was chromatographed on silica gel with hexane–ethyl acetate as eluant to give the *oxindole* (**48**) (82 mg), which was sublimed at 135—140 °C/1 mmHg followed by recrystallisation (68 mg, 69%) to give prisms, m.p. 167—169 °C (from EtOH) (Found: C, 78.8; H, 7.25; N, 6.8. $C_{14}H_{15}NO$ requires C, 78.8; H, 7.1; N, 6.6%); $\nu_{max.}$($CHCl_3$) 3 425, 3 180br, 1 710, and 1 610 cm^{-1}; $\nu_{max.}$(Nujol) 3 265, 1 700, 1 665, and 1 610 cm^{-1}; δ_H ($CDCl_3$; 400 MHz) 8.243 (1 H, br s, NH), 7.289 (1 H, d, *J* 7.5 Hz, H^c = oxindole 4-H), 7.177 (1 H, ddd, *J* 8, 7.5, and 1 Hz, oxindole 6-H, 6.998 (1 H, dd, *J* 8 and 7 Hz, oxindole 5-H), 6.863

(1 H, d, J 8 Hz, oxindole 7-H), 2.500 (1 H, s, 1-H), 2.261 (1 H, ddd, J 12, 5.5, and 3 Hz, 6-H_{endo}), 2.211 (1 H, d, J 2.5 Hz, 4-H), 2.100 (1 H, d, J 10 Hz, H^a), 1.895 (1 H, ddd, J 12.5, 3.5, and 3 Hz, 3-H_{exo}), 1.833 (1 H, dd, J 12.5 and 2 Hz, 3-H_{endo}), 1.63 (2 H, m, 5-H_{endo} and 6-H_{exo}), 1.473 (1 H, d, J 10 Hz, H^b), and 1.257 (1 H, m, 5-H_{exo}) (Found: M^+, 213.1153. $C_{14}H_{15}NO$ requires M, 213.1161); m/z 213 (25%, M^+) and 146 (100); $\delta_C(CDCl_3)$ 139.9, 130.2, 127.4, 123.5, 122.1, 108.9, 49.4, 42.0, 39.8, 37.4, 28.0, and 23.6 p.p.m.

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