Synthesis of (±)-(4a*S*, 13c*R*)- and (±)-(4a*R*, 13c*R*)-1,2,3,4,4a,13c-Hexahydro-5*H*-indazolo[2,3-*d*][1,4] benzodiazepin-6(7*H*)-ones

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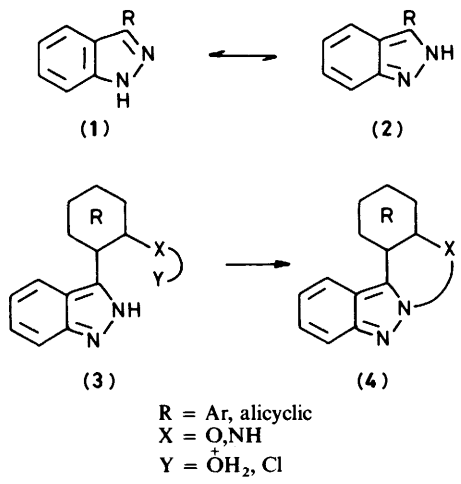
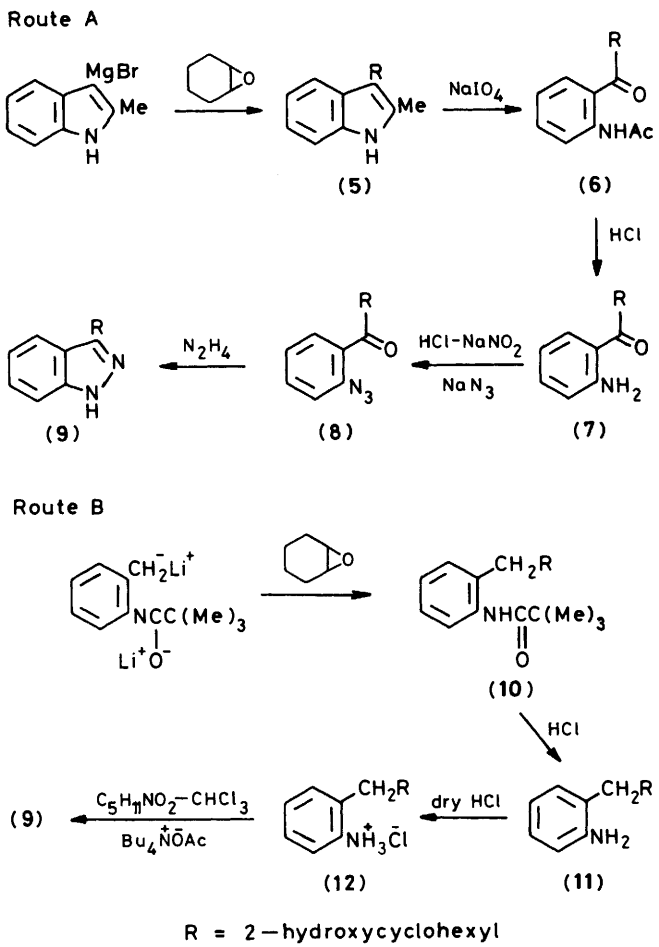
The synthesis of two novel hexahydro-5*H*-indazolo[2,3-*d*][1,4]benzodiazepin-6(7*H*)-ones is described. These fused heterocyclic benzodiazepines ensued from a general study into the synthesis of tetracyclic structures containing the indazole ring selectively bonded at the N-2 position.

The preparation of both benzodiazepines and diazepines with fused heterocyclic systems continues to generate much interest because of the possible psychopharmacological properties of such compounds.[1] Many heterocycles have been incorporated into these structures but, to the best of our knowledge, no syntheses of either benzodiazepines or diazepines fused to indazoles have been reported. We now describe the synthesis of the two stereoisomeric 1,2,3,4,4a,13c-hexahydro-5*H*-indazolo-[2,3-*d*][1,4]benzodiazepin-6(7*H*)-ones, (**20**) and (**21**), as part of a general investigation into the syntheses of novel heterocycles containing the indazole nucleus. In this work our syntheses are designed to utilise the tautomeric behaviour of the indazole nucleus (**1**) — (**2**) such that regioselective derivatisation of a suitably positioned ring substituent (**3**; X = O, NH) should then promote cyclisation through the N-2 of the indazole ring to form the tetracyclic structure (**4**).

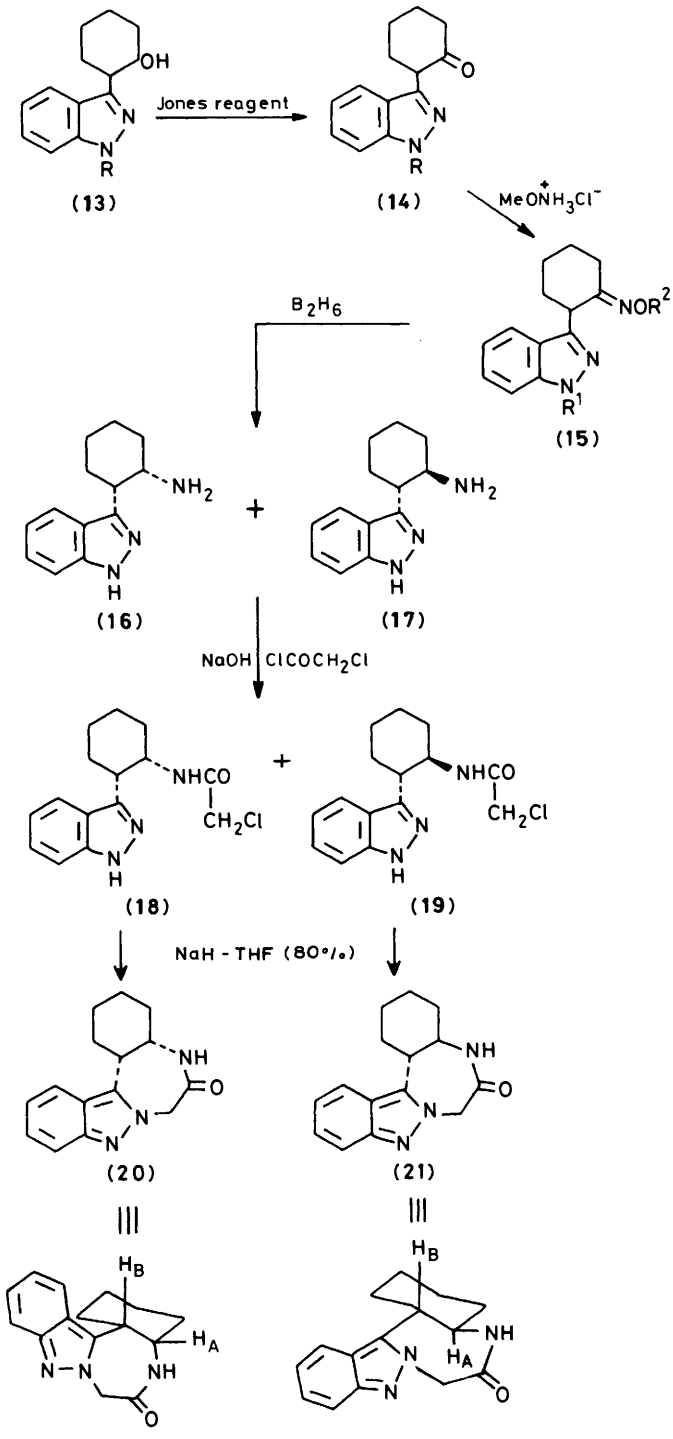


The route to the indazole-fused diazepines involved the synthesis of the intermediate 2-indazol-3-ylcyclohexanol (**9**). This was synthesized by two different routes (Scheme 1), both of which involved nucleophilic ring opening of cyclohexene oxide. The first approach was based on our related syntheses of 3-arylmethylindazoles[2] and 3-alicyclic(hydroxy)methylindazoles[3] as precursors to 4-substituted 1,2,3-benzotriazines, in which we had utilised the reaction between 2-methylindolylmagnesium bromide and suitable acid chlorides as the initial step. Since such Grignard reagents also react with oxiranes[4] it was thus possible to replace this step with the reaction between the same Grignard reagent and cyclohexene oxide (Route A). Although this reaction proceeded in poor yield no other difficulties were encountered in converting the indolylcyclohexanol (**5**) into the indazolylcyclohexanol (**9**) by the usual series of reactions,[2,3] the only surprising observation was the lack of formation of any conjugated ketone product during the acid hydrolysis of the amine protecting group (**6**) → (**7**). In the second approach to (**9**) (Route B) we utilised the dilithio anion derived from 2,2-dimethyl-*N*-*o*-tolylpropanamide. This reagent has already been shown to react with a variety of electrophiles[5] and we found that it also reacted smoothly with cyclohexene oxide to give the substituted cyclohexanol (**10**), which also showed no dehydration on acid hydrolysis to (**11**). Finally, in a typical indazole ring synthesis, the amine hydrochloride (**12**) was converted into the indazolylcyclohexanol (**9**) by diazotisation in chloroform in the presence of tetrabutylammonium acetate.[6] The products from both approaches were identical in all respects and shown to be *trans*-2-indazol-3-ylcyclohexanol by n.m.r. spectroscopy as described later. Also, since this compound (**9**) fits into our general scheme [(**3**) → (**4**)], we have studied several of its cyclisation reactions and these will be reported in another paper.[7]

Little is known about the stability of the *N*-protected or unprotected indazole ring to various oxidising and reducing agents,[8] and therefore our results and observations during the conversion of the indazolylcyclohexanol (**9**) into the indazolylcyclohexylamines (**16**) and (**17**) are of some contributory value to this area of indazole chemistry. We found that oxidation of the hydroxyindazole (**13**; R=H) with Jones' reagent[9] (10—30 min) gave 15—20% of the ketone (**14**; R=H) with no recoverable starting material; oxidation with 2,2-bipyridinium chlorochromate[10] (4—5 h) gave a small amount of ketone but largely degradation product; oxidation with Pfitzner-Moffatt reagent[11] (2—3 days) gave 15% of ketone together with unchanged starting material; and oxidation with silver carbonate[12] gave no reaction at all. In addition the unprotected ketone (**14**; R=H) proved to be very susceptible to auto-oxidation to a compound assigned as its *N*-oxide on the basis of mass spectrometric evidence [molecular ion of $\overset{+}{M}$ + 16 compared with (**14**; R=H)], and its facile reduction back to the ketoindazole using the Mo(V)Cl/Zn reagent.[13] Subsequently we found that oxidation of the N-1 acetylated or benzylated[14] hydroxyindazoles (**13**; R=Ac, CH_2Ph) with Jones' reagent gave good yields of the corresponding ketones, although surprisingly the *N*-benzylated oxoindazole proved to be unstable on storage. The results of our reduction studies on both the *N*-protected and unprotected oximes and methyl oximes (**15**; R^1=H, Ac, CH_2Ph; R^2=H, Me) can be summarised as follows. No reaction was observed in the attempted reduction of the unprotected oxime (**15**; R^1=R^2=H) with either sodium bis(2-methoxyethoxy)aluminium hydride, sodium in ethanol or diborane. Reduction of both the unprotected and protected methyl oximes (**15**; R^1=H, Ac, CH_2Ph; R^2=Me) however proceeded in high yield with diborane[15] with (**15**; R^1=Ac, Ac, R^2=Me) being the compound of choice owing to the stability of its ketone precursor and the



Scheme 1.

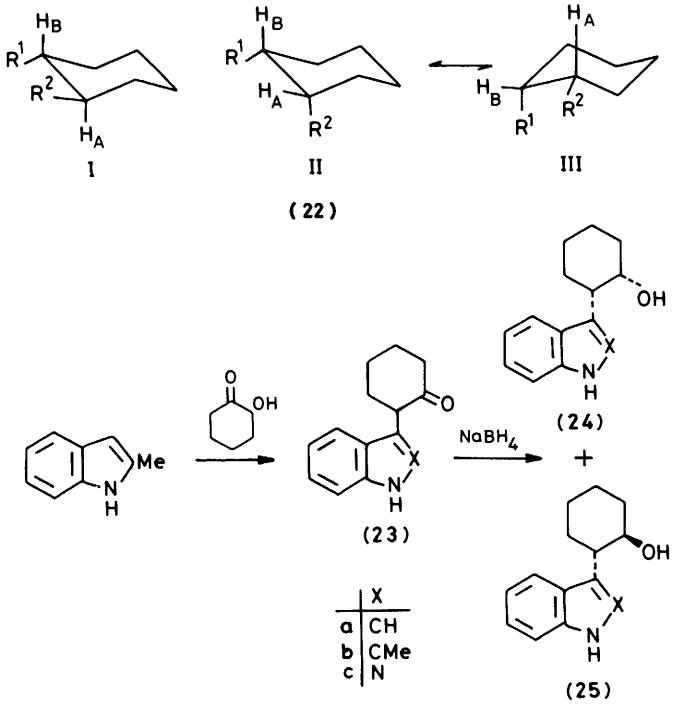


Scheme 2.*

facile removal of the acetyl group during hydrolysis of the borane addition complex to the amine. The stereoisomeric indazolylcyclohexylamines (**16**) and (**17**) thus produced (Scheme 2) could not be separated by chromatography but were converted into their chloroacetamides (**18**) and (**19**), which were separable, and were assigned as either the *cis* or *trans* isomer by n.m.r. spectroscopy. In theory this stage was critical since *N*-chloroacetylation could have taken place at either the NH_2 group of the cyclohexyl ring or at the NH of the indazole ring. In practice the former predominated to give (**18**) and (**19**) which on separate treatment with sodium hydride in THF ring-closed spontaneously, through N-2 of the indazole ring to give the two stereoisomeric indazole-fused benzodiazepines (**20**) and (**21**). Although small amounts of the di-*N*-chloroacetylated products were formed, it was found that the chloroacetyl group on the indazole nitrogen could be selectively removed by treatment with dilute aqueous sodium hydrogen carbonate.

The stereochemical relationship between the two cyclohexyl ring substituents in (**9** and **18**—**21**) was determined from an examination of the splitting patterns for their respective protons (**22**; H_A and H_B) in their high resolution ^1H n.m.r. spectra. These patterns had already been determined for *cis*- and *trans*-2-indol-3-ylcyclohexanols (**24a**) and (**25a**)[16] and we extended this work to include *cis*-and *trans*-2-(2-methylindol-3-yl)cyclohexanols (**24b**) and (**25b**). These were readily prepared by the reaction between 2-methylindole and 2-hydroxycyclohexanone[17] to give (**23b**), followed by reduction with sodium borohydride to the isomeric alcohols which were separated by preparative layer chromatography (Scheme 3). Similarly, reduction of the ketone (**23c**) gave *cis*- and *trans*-2-indazol-3-ylcyclohexanols (**24c**) and (**25c**). *trans*-Stereochemistry was then assigned to compounds (**25b**) and (**25c**) whose spectra showed H_A and H_B as triplets of

* The compounds (**16**)—(**21**), (**24**), and (**25**), depicted as *cis* or *trans* isomers, are racemic mixtures and only one enantiomer is shown.



Scheme 3.*

doublets with ΣJ *ca.* 25 Hz*, in agreement with that for (**25a**) and as expected for (**22-I**) with the 2-methylindol-3-yl and the indazol-3-yl substituents (R^1) and the hydroxy group (R^2) adopting the equatorial position. The spectrum for (**9**), from both synthetic routes, was identical with that of (**25c**) proving that it was the *trans* isomer, as expected from the route involving the stereospecific *trans* diaxial ring opening of cyclohexene oxide with 2-methylindolylmagnesium bromide, but of less predictable stereochemical assignment from the alternative approach.

cis Stereochemistry was assigned to (**24b**) and (**24c**) whose spectra showed H_A as a narrow multiplet with ΣJ *ca.* 9 Hz and H_B as a doublet of triplets with ΣJ *ca.* 16 Hz,* in agreement with that for (**24a**) and as expected for structure (**22-II**) with the 2-methylindol-3-yl and indazol-3-yl substituents (R^1) adopting the equatorial position in preference to the hydroxy group (R^2), which becomes axial.

Subsequently the more polar chloroacetamide (**19**) was shown to be the *trans* isomer since its spectra also showed ΣJ *ca.* 25 Hz for both H_A† and H_B. The less polar chloroacetamide (**18**) was then identified as the *cis* isomer, existing in a dynamic equilibrium between the two forms (**22-II**) $\rightleftharpoons$ (**22-III**) with neither the indazol-3-yl nor the chloroacetamide group taking preference for the equatorial position. The evidence for this assignment was that its spectrum showed similar values of ΣJ *ca.* 16 Hz for both H_A† and H_B which would arise if the system was considered as a dynamic equilibrium and the couplings observed assumed time-averaged values between those expected for H_A (equatorial) and H_B (axial) in (**22-II**) and those for H_A (axial) and H_B (equatorial) in (**22-III**).

Formation of the diazepine ring for both stereoisomers obviously imparted little strain into the cyclohexyl ring since the spectra show ΣJ *ca.* 25 Hz for H_A† and H_B in the *trans* isomer (**21**) and ΣJ *ca.* 9 Hz and ΣJ *ca.* 18 Hz for H_A† and H_B respectively in the *cis* isomer (**20**). The protons of the CH_2 group adjacent to the N-2 of the indazole ring were non-equivalent in both isomers with the upfield doublet experiencing a long range splitting of *ca.* 2 Hz.

Both (**20**) and (**21**) were evaluated for pharmacological activity and it was found that neither of them had benzodiazepine agonist activity but both had weak antagonist activity. The prime objective of this work was not the synthesis of pharmacologically active benzodiazepine-like compounds but the evaluation of the propensity of substituted indazoles such as (**18**) and (**19**) to form tetracyclic structures; having now demonstrated this, work is underway to synthesize and cyclise similar compounds with potentially greater pharmacological activity.

Experimental

M.p.s were determined on a Reichert Model 4065 micro hot-stage (Kofler) apparatus and are uncorrected. I.r. spectra were recorded for solutions in $CHCl_3$ on a Perkin-Elmer 157G spectrophotometer. ^1H N.m.r. spectra were taken on a Perkin-Elmer R12B spectrometer (low resolution) and on a Bruker WH 360 spectrometer (high resolution) for solutions in $CDCl_3$. Mass spectra were measured with an A.E.I. MS 30 instrument (low resolution) and an A.E.I. MS9 instrument (high resolution).

The 'usual work-up' referred to in the text involved extraction into a suitable solvent, washing with distilled water, drying over anhydrous sodium sulphate, filtering, and evaporating the solvent under reduced pressure. Most of the products thus obtained were preliminarily purified by vacuum chromatography. This involved adsorption of the material onto a sinter funnel packed with silica gel GF_{254} and then elution of the product with a suitable solvent under reduced pressure. Further purification using preparative thin layer chromatography (p.l.c.) was then employed for the preparation of samples for analysis and for the determination of spectroscopic data. All solvents were dried under the usual conditions prior to use and light petroleum refers to the fraction b.p. 60—80 °C. Ether refers to diethyl ether.

(±)-trans-2-(2-*Methylindol*-3-*yl*)*cyclohexanol* (**5**).—To the Grignard reagent, prepared by the slow addition of ethyl bromide (89.6 ml, 1.2 mol) to magnesium turnings (29.3 g, 1.2 mol) and a crystal of iodine in anhydrous ether (2 l) under nitrogen, was added a solution of 2-methylindole (150 g, 1.14 mol) in ether (1 l). The mixture was refluxed for 2 h, cooled in ice–water, and then a solution of cyclohexene oxide (118 g, 1.2 mol) in ether (1 l) was added dropwise to the vigorously stirred mixture during 1 h. The reaction mixture was then stirred for 1 h and left overnight at room temperature during which time a brown solid precipitated out. This solid was filtered off and dissolved in ethyl acetate and the solution was washed with 10% aqueous ammonium chloride and water and then dried over anhydrous sodium sulphate. Evaporation of the solvent gave a brown oil which was subjected to purification by vacuum chromatography. Elution with ether–ethyl acetate (1:1) gave the *product* (**5**) (78.5 g, 30%) as an off-white solid, m.p. 142—143 °C (white needles from ether–light petroleum); $\nu_{max.}$ 3 567 (OH) and 3 477 cm^{-1} (NH); δ [see values for (**25b**)] (Found: C, 78.7; H, 8.3; N, 6.1. $C_{15}H_{19}NO$ requires C, 78.6; H, 8.4; N, 6.1%).

* See Experimental for full assignment of *J* values.

† $J(N_H—H_A)$ values not included.

(±)-2-(2-*Acetamidobenzoyl*)*cyclohexanol* (**6**).—Sodium periodate (64.2 g, 0.3 mol) in water (700 ml) was added to a solution of (±)-*trans*-2-(2-methylindol-3-yl)cyclohexanol (**5**) (50 g, 0.2 mol) in methanol (500 ml) and the mixture stirred *continuously* at room temperature for *ca.* 3 days. Periodically the white precipitate of sodium iodate was filtered off and extra sodium periodate was added in portions (up to 21.4 g, 0.1 mol). After t.l.c. monitoring showed the reaction to have gone to completion, the methanol was removed under reduced pressure and the residue extracted with ethyl acetate, followed by evaporation of the solvent to give a brown oil. Vacuum chromatography using light petroleum–ethyl acetate (1:3) as the eluant gave the *product* (**6**) (40.5 g, 71%) as a white solid, m.p. 97—98 °C (white needles from ether–light petroleum); $\nu_{max.}$ 3 609 (OH), 1 691 (NHCOMe), and 1 645 cm^{-1} (CO); δ 4.06 (1 H, m, *H*COH) and 2.19 (3 H, s, Me) (Found: C, 68.9; H, 7.4; N, 5.4. $C_{15}H_{19}NO_3$ requires C, 68.9; H, 7.3; N, 5.4%).

(±)-2-(2-*Aminobenzoyl*)*cyclohexanol* (**7**).—Concentrated hydrochloric acid (150 ml) in water (200 ml) was added to a stirred solution of (±)-2-(2-acetamidobenzoyl)cyclohexanol (**6**) (35 g, 0.13 mol) in ethanol (600 ml) and the mixture refluxed for 3 h; it was then neutralised with 2M-sodium hydroxide. The usual work-up with ethyl acetate gave the *product* (**7**) as a pale yellow oil (25 g, 85%), $\nu_{max.}$ 3 603 (OH), 3 507 and 3 360 (NH_2), and 1 638 cm^{-1} (CO); δ4.99 (2 H, br, NH_2) and 4.08 (1 H, m, *H*COH); M^+, 219.1249 ($C_{13}H_{17}NO_2$ requires *M*, 219.1259).

(±)-2-(2-*Azidobenzoyl*)*cyclohexanol* (**8**).—Concentrated hydrochloric acid (200 ml) was added dropwise to a stirred solution of (±)-2-(2-aminobenzoyl)cyclohexanol (**7**) (21.8 g, 0.1 mol) in acetone (100 ml) at 0 °C. After the addition of the acid, the acetone was removed under reduced pressure and the solution cooled again to 0 °C. A solution of sodium nitrite (10 g, 0.15 mol) in water (50 ml) was then added to the reaction mixture followed after 30 min by the dropwise addition of a solution of sodium azide (13.0 g, 0.2 mol) in water (50 ml). The mixture was then stirred for a further 30 min, neutralised with 10% aqueous sodium hydrogen carbonate and worked up in the usual way with ethyl acetate to give the crude *product* (**8**) (20.5 g, 85%) as a brown oil. Purification by p.l.c. using ethyl acetate–light petroleum (1:1) as the developing solvent gave a sample of the unstable azide as a pale yellow oil, $\nu_{max.}$ 3 602 (OH), 2 135 (N_3), and 1 682 cm^{-1} (CO); δ 3.90 (1 H, m; *H*COH); $M^+ - N_2$, 217.1103 ($C_{13}H_{15}N_3O_2$ requires $M - N_2$, 217.1096).

(±)-trans-2-*Indazol*-3-*ylcyclohexanol* (**9**).—(±)-2-(2-Azidobenzoyl)cyclohexanol (**8**) (15.2 g, 0.06 mol) in absolute ethanol (400 ml) was refluxed with hydrazine hydrate (57.5 g, 1.2 mol) and glacial acetic acid (12 ml) for 5 h, followed by neutralisation with glacial acetic acid and removal of most of the ethanol under reduced pressure. The usual work-up with ethyl acetate then gave a brown oil which was purified by vacuum chromatography. Elution with ether–ethyl acetate (1:1) gave the *product* (**9**) (5.4 g, 40%) as a white solid, m.p. 142—143 °C (from ethyl acetate–light petroleum); $\nu_{max.}$ 3 591 (OH) and 3 473 cm^{-1} (NH); δ [see values for (**25c**)] (Found: C, 71.9; H, 7.4; N, 12.8. $C_{13}H_{16}N_2O$ requires C, 72.2; H, 7.5; N, 13.0%), M^+, 216.1260. ($C_{13}H_{16}N_2O$ requires *M*, 216.1263).

(±)-2-[2-(2,2-*Dimethylpropanamido*)*benzyl*]*cyclohexanol* (**10**).—A solution of 1.25M butyl-lithium in hexane (126 ml, 0.16 mol) was added *via* a syringe to a stirred solution of *N*-*o*-tolyl-2,2-dimethylpropanamide (10 g, 0.05 mol) in dry THF (100 ml) at 0 °C under nitrogen and the mixture stirred for 2 h. A solution of cyclohexene oxide (10.2 g, 0.1 mol) in dry THF (20 ml) was then added dropwise and the mixture stirred for 2 h at 0 °C and then at room temperature overnight. After the addition of ice-water the usual work-up with ether gave the *product* (**10**) as a white solid (9.9 g, 66%), m.p. 107—108 °C (from light petroleum); $\nu_{max.}$ 3 605 (OH), 3 320 (NH), and 1 660 cm^{-1} (CO); δ 3.18 (1 H, m, *H*COH), 2.97 (1 H, dd, *J* 13 and 4 Hz, *H*CHAr), 2.52 (1 H, dd, *J* 13 and 7 Hz, HC*H*Ar), and 1.32 (9 H, s, Me_3) (Found: C, 74.7; H, 9.6; N, 4.8. $C_{18}H_{27}NO_2$ requires C, 74.7; H, 9.3; N, 4.8%).

(±)-2-(2-*Aminobenzyl*)*cyclohexanol* (**11**).—A solution of (±)-2-[2-(2,2-dimethylpropanamido)benzyl]cyclohexanol (**10**) (8.5 g, 0.03 mol) in ethanol (100 ml) was refluxed with concentrated hydrochloric acid (40 ml) and water (50 ml) for *ca.* 2 days. The solution was then neutralised with 2M sodium hydroxide, diluted with water, and extracted into ether. The usual work-up gave a crude solid which was purified by vacuum chromatography. Elution with ether–light petroleum (1:1) gave the *product* (**10**) as a white powder (4.9 g, 82%), m.p. 77—78 °C (from ether); $\nu_{max.}$ 3 610 (OH), 3 440, and 3 370 cm^{-1} (NH_2); δ 3.65 (2 H, br, NH_2), 3.25 (1 H, t d, *J* 9, 9, and 4 Hz, *H*COH), 2.97 (1 H, dd, *J* 13 and 4 Hz, *H*CHAr), 2.36 (1 H, dd, *J* 13 and 7 Hz, HC*H*Ar) (Found: C, 76.2; H, 9.5; N, 6.8. $C_{13}H_{19}NO$ requires C, 76.1; H, 9.3; N, 6.8%).

(±)-trans-2-*Indazol*-3-*ylcyclohexanol* (**9**).—(±)-2-(2-Hydroxy-cyclohexylmethyl)anilinium chloride (**12**) (4.4 g, 96%) was prepared by bubbling dry hydrogen chloride gas through a solution of (±)-2-(2-aminobenzyl)cyclohexanol (**11**) (4 g) in dry ether. The hydrochloride (**12**) was filtered off, suspended in chloroform (10 ml), and stirred with pentyl nitrite (3.8 g, 0.03 mol) at room temperature for 30 min. Tetrabutylammonium acetate (10 g, 0.03 mol) in chloroform (20 ml) was added and the mixture stirred for 2 h. Water was then added after which the chloroform layer was separated, washed with 2M sodium hydroxide and water, dried, and evaporated. Purification by vacuum chromatography, using ether–ethyl acetate (1:1) as the eluant, gave the *product* (**9**) as a white solid [2.1 g, 50% from (**11**)]. The product was identical with that prepared from (**8**).

(±)-2-*Indazol*-3-*ylcyclohexanone* (**14**; R=H).—Chromic acid (Jones reagent) was added dropwise to a stirred solution of (±)-*trans*-2-indazol-3-ylcyclohexanol (**9**) (2.2 g, 0.01 mol) in acetone (50 ml) at 0 °C until it remained orange. After 10—30 min (t.l.c. monitoring) the excess of reagent was destroyed by the addition of sulphur dioxide-saturated acetone followed by dilution with water. The usual work-up with ethyl acetate then gave a yellow oil which was purified by p.l.c. using ethyl acetate–light petroleum (1:1) as the developing solvent. This gave the *product* (**14**; R=H) as an oil (0.44 g, 20%); $\nu_{max.}$ 3 469 (NH) and 1 711 (CO); δ 4.20 (1 H, m, CHCO); M^+, 214.1110 ($C_{13}H_{14}N_2O$ requires *M*, 214.1106).

The pure ketone (**14**; R=H) was found to be unstable on storage at 0 °C. T.l.c. monitoring showed the formation of a less polar product which was separated by p.l.c. (ether–benzene, 1:1) and obtained as an oil, $\nu_{max.}$ 1 715 cm^{-1} (CO) (Found: M^+, 230.1058. $C_{13}H_{14}N_2O_2$ requires *M*, 230.1055).

The above oil (0.2 g, 0.9 mmol) was dissolved in THF (2 ml) and added to the reagent[13] prepared by the addition of water (2 ml) and zinc dust (0.2 g) to molybdenum chloride (0.4 g) in THF (5 ml). After refluxing for 3 h, the solution was made alkaline with 2M sodium hydroxide and the THF evaporated off under reduced pressure. The usual work-up of the residue with ethyl acetate gave the product as an oil (0.1 g) that was identical in all respects with (±)-2-indazol-3-ylcyclohexanone (**14**; R=H).

(±)-2-(1-*Acetylindazol*-3-*yl*)*cyclohexanol* (**13**; R=Ac).—A solution of (±)-*trans*-2-indazol-3-ylcyclohexanol (**9**) (4 g, 0.019

mol) in dry THF (50 ml) was slowly added to a suspension of sodium hydride (1 g, 0.021 mol) in dry THF (20 ml) at 0 °C under nitrogen. Acetyl chloride (1.6 g, 0.02 mol) in THF (5 ml) was then added and the mixture was stirred for 30 min at 0 °C and 1 h at 40 °C followed by addition to cold water. The usual work-up with ethyl acetate then gave the intermediate *product* (**13**; R=Ac) as a white powder (4.1 g, 87%), m.p. 97—98 °C (from ether); $\nu_{max.}$ 3 590 (OH) and 1 715 cm^{-1} (CO); δ 4.10 (1 H, m, *H*COH) and 2.70 (3 H, s, Me); *m/z*, 258.

(±)-2-(1-*Acetylindazol*-3-*yl*)*cyclohexanone* (**14**; R=Ac).—This compound was prepared as for (**14**; R=H) using Jones reagent and (±)-2-(1-acetylindazol-3-yl)cyclohexanol (**13**; R=Ac) (4 g) in acetone (300 ml). The usual work-up with ether gave the *product* (**14**; R=Ac) as a white solid (3.5 g, 87%), m.p. 102—104 °C (from ether–light petroleum); $\nu_{max.}$ 1 713 cm^{-1} (CO); δ 4.11 (1 H, m, CHCO), 2.71 (3 H, s, Me); M^+, 214.1110. [$C_{15}H_{16}N_2O_2$ requires M − (H_2CCO), 214.1106] (Found: C, 70.0; H, 6.2; N, 10.7. $C_{15}H_{16}N_2O_2$ requires C, 70.3; H, 6.3; N, 10.9%).

(±)-2-(1-*Benzylindazol*-3-*yl*)*cyclohexanol* (**13**; R=CH_2Ph).—This compound was prepared as for (**13**; R=Ac) from (±)-*trans*-2-indazol-3-ylcyclohexanol (**9**) (1.0 g, 4.6 mmol) and benzyl bromide (0.8 g, 4.6 mmol). The usual work-up with ether gave an oil which was purified by p.l.c. using benzene–ether (1:1) as developing solvent. This gave the intermediate *product* (**13**; R=CH_2Ph) as a white solid (1.1 g, 81%), m.p. 92—93 °C; $\nu_{max.}$ 3 585 cm^{-1} (OH); δ 7.94—7.81 (1 H, m, ArH), 7.43—7.01 (3 H, m, ArH), 7.25 (5 H, s, ArH), 5.55 (2 H, s, CH_2), 4.15 (1 H, m, C*H*OH), and 2.95 (1 H, m, HCC=N).

(±)-2-(1-*Benzylindazol*-3-*yl*)*cyclohexanone* (**14**; R=CH_2Ph).—This compound was prepared as for (**14**; R=H) using Jones' reagent and (±)-2-(1-benzylindazol-3-yl)cyclohexanol (0.5 g) in acetone (35 ml). The usual work-up with ether gave the *product* (**14**; R=CH_2Ph) as an oil (0.40 g, 80%) which also proved to be unstable and susceptible to oxidation on storage at 0 °C; $\nu_{max.}$ 1 712 cm^{-1} (CO); δ 8.43 (1 H, m, ArH), 7.22—7.00 (3 H, m, ArH) 7.32 (5 H, s, ArH), 5.64 (2 H, s, CH_2), and 4.10 (1 H, m, CHCO); *m/z* 304 (on storage a less polar product was formed, *m/z*, 320).

(±)-cis- *and* trans-2-*Indazol*-3-*ylcyclohexanol* (**24c**) *and* (**25c**).—Sodium borohydride (0.15 g, 3.7 mmol) was added in portions to a solution of (±)-2-indazol-3-ylcyclohexanone (**23c**) (0.4 g, 1.87 mmol) in ethanol (50 ml) and the mixture was refluxed gently for 1 h. After cooling and the addition of water the ethanol was evaporated under reduced pressure. The usual work-up with ethyl acetate gave the *products* (**24c**) and (**25c**) (0.36 g, 90%) which were separated by p.l.c. using ethyl acetate–light petroleum (3:1) as the developing solvent. The more polar isomer was found to be (±)-*trans*-2-indazol-3-ylcyclohexanol (**25c**) which was identical in all respects to (**9**); δ 7.76 (1 H, d, *J* 6 Hz, ArH), 7.39—7.09 (3 H, ArH), 4.10 (1 H, td, *J* 10, 10, and 4 Hz, *H*COH), and 3.04 (1 H, td, *J* 10, 10, and 4 Hz, HCC=N).

The less polar isomer was found to be (±)-*cis*-2-indazol-3-ylcyclohexanol (**24c**), m.p. 116—118 °C; $\nu_{max.}$ 3 590 (OH) and 3 472 cm^{-1} (NH); δ 7.71 (1 H, d, *J* 6 Hz, ArH), 7.46—7.12 (3 H, ArH), 4.34 (1 H, m, *J* 3, 3, and 3 Hz, *H*COH), and 3.22 (1 H, dt, *J* 10, 3, and 3 Hz, *H*CC=N) (Found: C, 72.1; H, 7.2; N, 13.0. $C_{13}H_{16}N_2O$ requires C, 72.2; H, 7.5; N, 13.0%); M^+, 216.1263 ($C_{13}H_{16}N_2O$ requires *M*, 216.1263).

(±)-2-(2-*Methylindol*-3-*yl*)*cyclohexanone* (**23b**).—2-Methylindole (0.5 g, 3.8 mmol) and 2-hydroxycyclohexanone (0.85 g, 7.6 mmol) were added to a mixture of glacial acetic acid (24 ml) and 2M phosphoric acid (6 ml) heated to 100 °C.[17] The mixture was refluxed for 1 h and then poured onto ice–aqueous ammonia. The usual work-up with ethyl acetate then gave the *product* (**23b**) as a white solid (0.6 g, 71%), m.p. 139—140 °C (from ether–light petroleum); $\nu_{max.}$ 3 470 (NH) and 1 709 cm^{-1} (CO); δ, 7.95 (1 H, b, NH), 3.71 (1 H, m, HCC=O), and 1.92 (3 H, s, Me) (Found: C, 79.0; H, 7.4; N, 6.0. $C_{15}H_{17}NO$ requires C, 79.3; H, 7.5; N, 6.2%).

(±)-cis- and trans-2-(2-*Methylindol*-3-*yl*)*cyclohexanol* (**24b**) *and* (**25b**).—These compounds were prepared as for (**24c**) and (**25c**) using sodium borohydride (0.1 g, 2.6 mmol) and 2-(2-methylindol-3-yl)cyclohexanone (**23b**) (0.4 g, 1.7 mmol) in ethanol (50 ml). The usual work-up with ethyl acetate gave the *products* (**24b**) and (**25b**) (0.35 g, 85%) which were separated by p.l.c. using ether–light petroleum (1:1) as the developing solvent. The more polar isomer was found to be (±)-*trans*-2-(2-methylindol-3-yl)cyclohexanol (**25b**) which was identical in all respects with (**5**); δ 7.86 (1 H, br, NH), 7.65 (1 H, d, *J* 7 Hz, ArH), 7.29—7.02 (3 H, ArH), 4.03 (1 H, td, *J* 10, 10 and 4 Hz, *H*COH), 2.65 (1 H, td, *J* 10, 10, and 4 Hz *H*CC=CMe), and 2.42 (3 H, s, Me) [*cf.* δ 3.76 (1 H, td, *J* 10, 10, and 4 Hz, *H*COH) for (**25a**)].[16]

The less polar isomer was found to be (±)-*cis*-2-(2-methylindol-3-yl)cyclohexanol (**24b**), m.p. 182—184 °C; $\nu_{max.}$ 3 566 (OH) and 3 477 cm^{-1} (NH); δ 7.87 (1 H, br, NH), 7.73 (1 H, d, *J* 7 Hz, ArH), 7.26—7.02 (3 H, ArH), 4.01 (1 H, m, *J* 3, 3, and 3 Hz, *H*COH), 3.00 (1 H, dt, *J* 10, 3, and 3 Hz, *H*CC=CMe), and 2.44 (3 H, s, Me) [*cf.* δ 4.18 (1 H, m, *J* 2.3, 2.3, and 2.3 Hz, *H*COH) for (**24a**)][16] (Found: C, 78.3; H, 8.0; N, 5.8. $C_{15}H_{19}NO$ requires C, 78.7; H, 8.3; N, 6.1%); M^+, 229.1460 ($C_{15}H_{19}NO$ requires *M*, 229.1467).

(±)-2-(1-*Acetylindazol*-3-*yl*)*cyclohexanone O-Methyloxime* (**15**; R^1=Ac, R^2=Me).—*O*-Methoxylamine hydrochloride (1.5 g, 18 mmol) was added to a stirred solution of (±)-2-(1-acetylindazol-3-yl)cyclohexanone (**14**; R=Ac) (3 g, 11.7 mmol) in pyridine (50 ml) and the mixture stirred overnight at room temperature. After removal of the pyridine under reduced pressure the usual work-up with ether gave the *product* (**15**; R^1=Ac, R^2=Me) as a white solid (3.1 g, 92%), m.p. 96—98 °C (from ether–light petroleum); $\nu_{max.}$ 1 708 (CO) and 1 040 cm^{-1} (NOMe); δ 4.10 (1 H, m, *H*CCNOMe), 3.72 (3 H, s, OMe), and 2.74 (3 H, s, Me) (Found M^+, 285.1482. $C_{16}H_{19}N_3O_2$ requires *M*, 285.1477).

(±)-cis- *and* trans-2-*Indazol*-3-*ylcyclohexylchloroacetamide* (**18**) *and* (**19**).—Borane–dimethyl sulphide (1.3 g, 17 mmol diborane) was added slowly to a solution of (±)-2-(1-acetylindazol-3-yl)cyclohexanone *O*-methyl oxime (**15**) (2.5 g, 8.7 mmol) in THF (40 ml) at 0 °C under nitrogen. The reaction mixture was then refluxed for 3 h, cooled to 0 °C, and diluted by the dropwise addition of water (10 ml) and dilute hydrochloric acid (10 ml). The mixture was then refluxed again for 2 h, diluted with water, and basified with 2M-sodium hydroxide. The usual work-up with chloroform gave an inseparable mixture of (±)-*cis*- and *trans*-2-indazol-3-ylcyclohexylamines (**16**) and (**17**) (1.3 g, 59%) as an intermediate yellow oil. 0.5M-Sodium hydroxide (10 ml) and chloroacetyl chloride (0.7 g, 6 mmol) were then added to the yellow oil (1.3 g, 6.0 mmol) dissolved in chloroform and the reaction mixture was stirred at room temperature for 2 h. The solution was poured into water and subjected to the usual work-up with chloroform to give the products (**18**) (60%) and (**19**) (40%), (1.2 g, 72%) which were separated by p.l.c. using benzene–ether (1:1) as the developing solvent. The p.l.c. separation also yielded small amounts of two less polar products which were identified as the dichloroacetylated isomers, $\nu_{max.}$ 3 405 (NHCO), 1 722 (NCO), and 1 665 cm^{-1} (NHCO). On dissolution in ethanol and treatment with a few drops of 2M-sodium hydrogen carbonate solution for *ca.* 15 min, t.l.c. monitoring indicated hydrolysis to give (**18**) and (**19**).

The more polar isomer was found to be (±)-*trans*-2-indazol-3-ylcyclohexylchloroacetamide (**19**), m.p. 155—157 °C (from ether); $\nu_{max.}$ 3 460 (NH), 3 400 (NHCO), and 1 665 cm^{-1} (CO); δ 7.78 (1 H, d, *J* 7 Hz, ArH), 7.44—7.10 (3 H, ArH), 6.47 (1 H, br d, *J* 8 Hz, NHCO), 4.22 (1 H, m, *J* 11, 11, 8, and 4 Hz *H*CNH), 3.77 (1 H, d, *J* 12 Hz, *H*CHCl), 3.53 (1 H, d, *J* 12 Hz, HC*H*Cl), 3.10 (1 H, td, *J* 11, 11, and 4 Hz, HCC=N); M^+, 293.1111 and 291.1145 ($C_{15}H_{18}{}^{37}ClN_3O$ requires *M*, 293.1109 and $C_{15}H_{18}{}^{35}ClN_3O$ requires *M*, 291.1138) (Found: C, 61.6; H, 6.1; N, 14.2. $C_{15}H_{18}{}^{35}ClN_3O$ requires C, 61.8; H, 6.2; N, 14.4%).

The less polar isomer was found to be (±)-*cis*-2-indazol-3-ylcyclohexylchloroacetamide (**18**), m.p. 122—124 °C (from ether); $\nu_{max.}$ 3 470 (NH), 3 400 (NHCO), and 1 660 cm^{-1} (CO); δ 7.68 (1 H, d, *J* 7 Hz, ArH), 7.52 (1 H, br d, *J* 8 Hz, NHCO), 7.50—7.10 (3 H, m, ArH), 4.38 (1 H, m, *J*, 4, 4, 8, and 8 Hz, *H*CNH), 3.95 (1 H, d, *J* 11 Hz, *H*CHCl), 3.83 (1 H, d, *J* 11 Hz, HC*H*Cl), and 3.66 (1 H, m, *J*, 4, 4, and 8 Hz, HCC=N); M^+, 291.1131 ($C_{15}H_{18}{}^{35}ClN_3O$ requires *M*, 291.1138) (Found: C, 61.7; H, 6.3; N, 14.4. $C_{15}H_{18}{}^{35}ClN_3O$ requires C, 61.8; H, 6.2; N, 14.4%).

±-(4a*R*,13c*R*)-1,2,3,4,4a,13c-*Hexahydro*-5H-*indazolo*[2,3-d][1,4]*benzodiazepin*-6(7H)-*one* (**21**).—A solution of (±)-*trans*-2-indazol-3-ylcyclohexylchloroacetamide (**19**) (0.5 g, 1.7 mmol) in dry THF (30 ml) was added dropwise to a suspension of sodium hydride (50 mg, 2 mmol) in dry THF (20 ml) at 0 °C under nitrogen. The reaction mixture was stirred for 1 h at room temperature and 30 min at 50 °C, cooled, and then poured into water. The usual work-up with chloroform gave the *product* as a white powder (0.35 g, 79%), m.p. 190—192 °C (from ether); $\nu_{max.}$ 3 391 (NHCO) and 1 678 cm^{-1} (CO); δ 7.65—7.58 (2 H, m, ArH), 7.28—6.97 (2 H, m, ArH), 5.99 (1 H, br d, *J* 5 Hz, NH), 5.49 (1 H, d, *J* 13 Hz, *H*CHCO), 5.22 (1 H, dd, *J* 13 and 2 Hz, HC*H*CO), 3.80 (1 H, m, *J* 11, 11, 5, and 3 Hz, *H*CNH), 3.28 (1 H, td, *J* 11, 11, and 3 Hz, HCCN); M^+, 255.1370 ($C_{15}H_{17}N_3O$ requires *M*, 255.1372) (Found: C, 70.5; H, 6.5; N, 16.4. $C_{15}H_{17}N_3O$ requires C, 70.6; H, 6.7; N, 16.5%).

±-(4a*R*,13c*S*)-1,2,3,4,4a,13c-*Hexahydro*-5H-*indazolo*[2,3-d][1,4]*benzodiazepin*-6(7H)-*one* (**20**).—This compound was prepared as for (**21**) from (±)-*cis*-2-indazol-3-ylcyclohexylchloroacetamide (**18**) (0.35 g, 1.2 mmol). The product (**20**) was obtained as a white solid (0.25 g, 82%), m.p. 251—253 °C; $\nu_{max.}$ 3 400 (NHCO) and 1 680 cm^{-1} (CO); δ 7.63—7.51 (2 H, m, ArH), 7.28—7.00 (2 H, m, ArH), 6.45 (1 H, br d, *J* 5 Hz, N*H*), 5.41 (1 H, d, *J* 13 Hz, *H*CHCO), 5.28 (1 H, dd, *J* 13 and 2 Hz, HC*H*CO), 4.40 (1 H, m, *J* 5, 3, 3, and 3 Hz, *H*CNH), and 3.45 (1 H, dt, *J* 11, 3, and 3 Hz, HCCN); M^+, 255.1378 ($C_{15}H_{17}N_3O$ requires *M*, 255.1372) (Found: C, 70.3; H, 6.4; N, 16.3; $C_{15}H_{17}N_3O$ requires C, 70.6; H, 6.7; N, 16.5%).

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