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SOME *CIS*- AND *TRANS*-DECAHYDROISOQUINOLINE DERIVATIVES AND THEIR NMR SPECTRA

AN INTERESTING STABLE TWIST-BOAT FUSED CYCLOHEXANE

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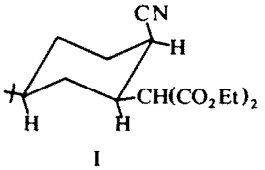
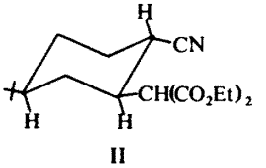
Abstract—One of the two possible *cis*-6-t-butyldecahydroisoquinolines and *trans*-6-t-butyldecahydroisoquinoline have been synthesized from the appropriate 2-cyanocyclohexylmalonate derivatives. The stereochemistries of the intermediate 6-t-butyl-4-carbethoxy-3-oxodecahydroisoquinolines (IVa and IX) have been supported by NMR spectroscopy. 6-t-Butylisoquinoline has been prepared but its reduction gave products which could not be resolved. Reductive cyclization of ethyl 4-t-butyl(*e*)-2-carbethoxymethyl(*a*)-1-cyano(*a*)cyclohexanecarboxylate(*e*) (III) gave 6-t-butyl-9-carbethoxy-3-oxodecahydroisoquinoline (XV) in which the cyclohexane ring is in a twist-boat conformation and the pyridone is in a half chair conformation. A first-order analysis of the NMR spectrum of XV confirmed this geometry. Hydrolysis of XV gave an acid which could not be decarboxylated. Various attempts to arrive at 6-t-butylisoquinoline by alternate routes are described.

THE addition of diethyl malonate to 4-t-butyl-1-cyanocyclohexene afforded cyanomalonates I and II and ethyl 4-t-butyl(*e*)-2-carbethoxymethyl(*a*)-1-cyano(*a*)cyclohexanecarboxylate(*e*) (III) whose structures and stereochemistry were established unambiguously.[1] It has previously been shown that diethyl *cis*- and *trans*-2-cyanocyclohexylmalonate can be reduced stereospecifically to the corresponding decahydroisoquinoline derivatives,[2] and this has now been extended to compounds I, II and III.



I



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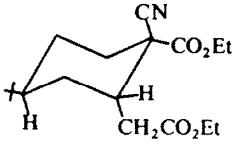
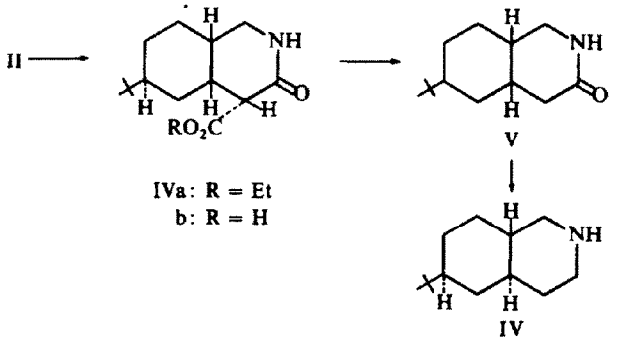


III

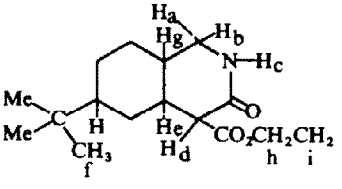
Catalytic reduction of II over Raney nickel at 115° and a pressure of 1450 psi gave *trans*-6-t-butyl-4-carbethoxy-3-oxodecahydroisoquinoline (IVa) in high yield. This was saponified to give IVb which underwent decarboxylation very readily and afforded *trans*-6-t-butyl-3-oxodecahydroisoquinoline (V). LAH reduction of V gave *trans*-6-t-butyldecahydroisoquinoline (VI). The geometry of IVa was confirmed by a first-order analysis of its NMR spectra in (i) CCl_4, (ii) CCl_4 and D_2O, and (iii) CCl_4 containing NaOD in D_2O. The spectral data and the assignments are summarized in Table 1. The ester group gave rise to the usual 2H quartet at 5·83 τ (J = 7 c/s) ($CO_2C\underline{H}_2CH_3$) and a 3H triplet at 8·70 τ ($CO_2CH_2C\underline{H}_3$). A 1H doublet at 1·88 τ



(J_{ac} = 3 c/s) was assigned to N–$\underline{H}_c$ since it was removed on treatment of the solution with D_2O. A 2H AB quartet at 6·73 τ_a and 7·05 τ_b (J_{ab} = 12 c/s) was assigned to the non-equivalent protons on C_1 (CH_aH_bN). Each peak on the A side was a triplet (J = 3 c/s) which, on treatment of the solution with D_2O collapsed to a doublet (J = 4 c/s). These protons are probably unequally shielded by the lone pair of electrons on the adjacent nitrogen atom. The observed splitting may be explained if it is assumed that H_a (in VII) is coupled to H_g (J_{ag} = 4 c/s) and to H_c ($J_{ac} \sim$ 3 c/s) so that each gave rise to a quartet with the centre lines unresolved, hence appearing as a triplet. In the N-deuterated compound H_a was only coupled measurably to H_g (J_{ag} = 4 c/s). The B side of the AB quartet (7·05 τ) appeared as a triplet (J = 10·5 c/s) (relative intensities ca. 2:3:1) and this was not changed by treating the compound with D_2O in NaOD. It was concluded, therefore, that H_b was not coupled, or only very weakly so, to H_c ($J_{bc} \simeq 0$ c/s), but that it was coupled to H_g (J_{bg} = 10·5 c/s). The central band of the observed triplet consists of two unresolved lines ca. 1·5 c/s apart, as illustrated in Fig. 1. A 1H doublet at 7·26 τ (J_{de} = 11·8 c/s) was not affected on treatment of the compound with D_2O, but was removed completely when the carbon tetrachloride solution was treated with NaOD in D_2O. This doublet can, therefore, be assigned with confidence to the active methylene C_4-H_d proton.

The conformation and approximate dihedral angles in IVa (VII) can be estimated using the Karplus relationship,[3] but modified as was done for the 2-substituted 3-ketosteroids:[4, 5]

$$J = 12{\cdot}4 \cos^2 \phi \quad (0° \leqslant \phi \leqslant 90°)$$
$$J = 14{\cdot}3 \cos^2 \phi \quad (90° \leqslant \phi \leqslant 180°)$$



VII

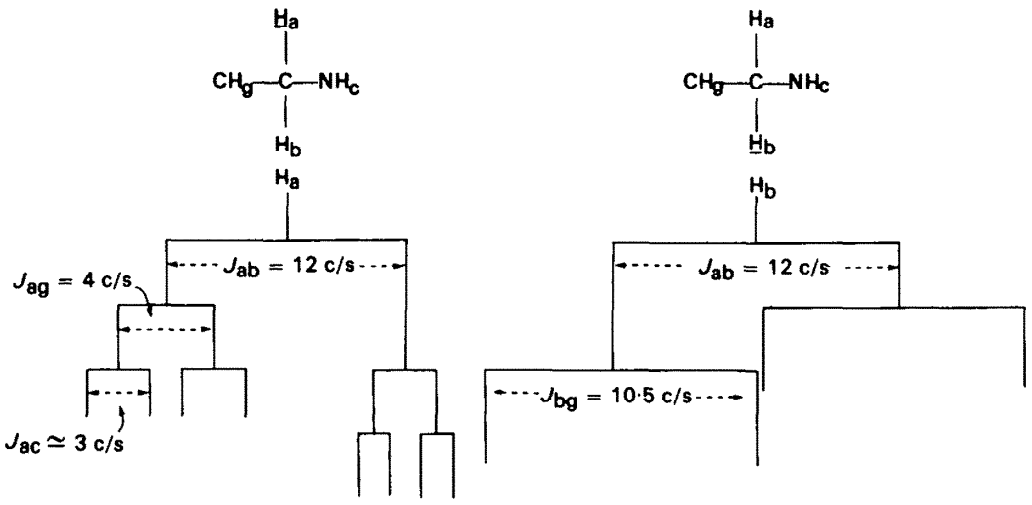
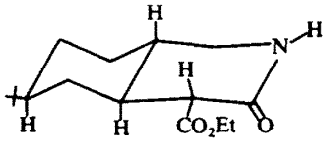


FIG. 1. First-order analysis at C_1 methylene AB quartet in VII

A better fit would undoubtedly be obtained if one could modify the curve further to account for the influence of the elctronegativity of the nitrogen atom upon the magnitude of the coupling constants.[6] Unfortunately, substituted lactams of known conformation are not available as model compounds. The conformation which gave the closest fit (using Dreiding models) with the derived dihedral angles between protons H_a–H_c, H_a–H_g, H_b–H_c, H_b–H_g and H_d–H_e when all of these are taken into consideration is one in which the homocyclic and heterocyclic rings were in chair and half-chair conformations, respectively, with a *trans* ring junction (VIII).*

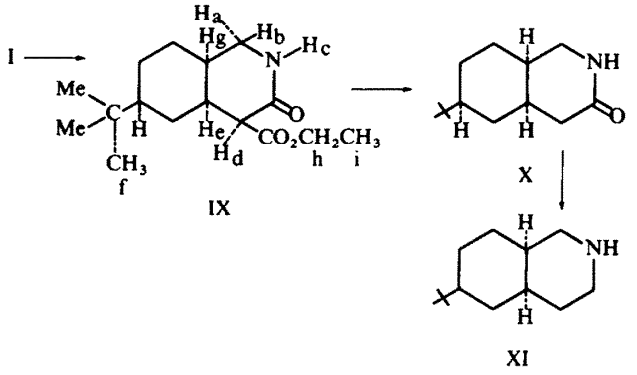


VIII

A similar sequence of reactions was carried out with I. Catalytic reduction gave IX which was hydrolyzed and decarboxylated to the *cis*-lactam X. Reduction with LAH gave *cis*-6-t-butyldecahydroisoquinoline (XI).

Again, the NMR spectrum of the β-amidoester IX provided confirmation of the assigned geometry. Lines at 5·85 τ (2H quartet, J = 7 c/s) and 8·72 τ (3H triplet,

* The dihedral angles between the various protons calculated on the basis of the appropriate coupling constants were as follows (angles estimated from a Dreiding model for a chair, half-chair conformation are given in brackets): H_a–H_c 61° or 117° (40°); H_a–H_g 56° or 122° (130°); H_b–H_c 90° (80°); H_b–H_g 23° or 149° (10°); H_d–H_e 18° or 150° (170°). Reasonable agreement between the calculated and the estimated values was also found for a boat, half-chair conformation, but this was rejected since in such a conformation the t-butyl group would have to be almost axial. Other conformations had one or two dihedral angles which fitted much better with those calculated using the modified Karplus curve, but the rest were not compatible at all with the calculated angles.



J = 7 c/s) were observed for the ethyl ester group at C_4, as was a 9H singlet at 9·13 τ for the t-butyl group. The amide N–H proton gave a 1H doublet at 1·83 τ (J_{bc} = 4 c/s) which vanished when the solution was treated with D_2O. The C_1 methylene group gave rise to an AB quartet at 6·47 τ_a and 6·99 τ_b (J_{ab} = 12 c/s). Each branch of the B side was a doublet (J_{bc} = 4 c/s) which collapsed to singlets when D_2O was added to the solution, indicating coupling of H_b with H_c but not with H_g ($J_{bg} \simeq 0$ c/s). Each branch of the A side of the quartet was a doublet (J = 3 c/s), unchanged on N-deuteration. There must be no, or almost no coupling between H_a and H_c ($J_{ac} \simeq 0$ c/s), and J_{ag} = 3 c/s. These splittings are illustrated in Fig. 2. A 1H broad doublet

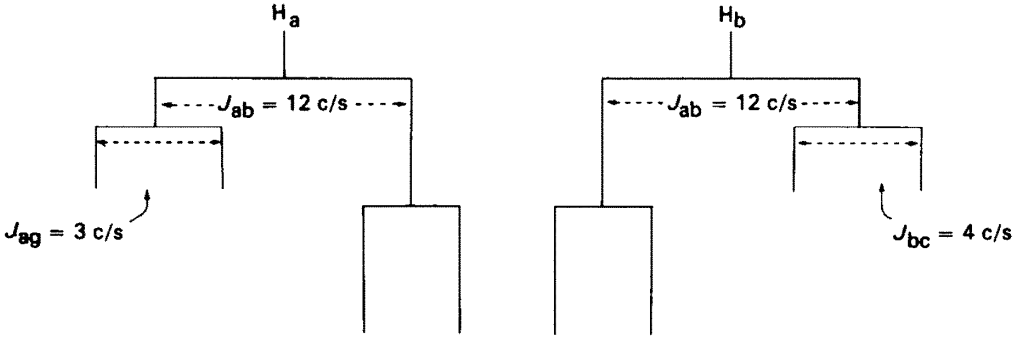


FIG. 2. First-order analysis of C_1 methylene AB quartet in IX.

at 7·51 τ (J = 11·5 c/s) was not eliminated on treatment of the solution with D_2O, but became a broad singlet when NaOD was added. It was thus assigned to H_e. The 1H doublet at 6·7 τ (J = 11·5 c/s) was also not affected by the addition of D_2O but vanished altogether when NaOD was added; it was thus assigned to H_d (coupled with H_e). The data and assignments are summarized in Table 2.

Using the modified Karplus curve the dihedral angles between H_a–H_c, H_a–H_g, H_b–H_c, H_b–H_g, and H_d–H_e could be estimated approximately. The conformation which gave the best (but not very close) fit with the derived dihedral angles was that in which the homocyclic and heterocyclic rings were in chair and twist-boat conformations, respectively, with a *cis*-ring junction (XII). The very approximate nature

TABLE 1. NMR SPECTRUM OF *trans*-6-t-BUTYL-4-CARBETHOXY-3-OXODECAHYDROISOQUINOLINE (VII) IN CCl_4 (τ VALUES)

H_a and H_b	H_c	H_d	H_e	H_f	H_g	H_h	H_i
AB quartet at 6·73 τ_a and 7·05 τ_b	1·88 doublet (J_{ac} = 3 c/s)	7·26 doublet (J_{de} = 11·8 c/s)	>7·26 not identified	9·09 singlet	>7·8 not identified	5·83 quartet (J_{hi} = 7 c/s)	8·70 triplet (J_{hi} = 7 c/s)

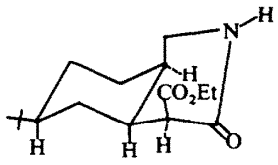
TABLE 2. NMR SPECTRUM OF *cis*-6-t-BUTYL-4-CARBETHOXY-3-OXODECAHYDROISOQUINOLINE (IX) IN CCl_4 (τ VALUES)

H_a and H_b	H_c	H_d	H_e	H_f	H_g	H_h	H_i
AB quartet at 6·47 τ_a and 6·99 τ_b	1·83 doublet (J_{bc} = 4 c/s)	6·7 doublet (J_{de} = 11·5 c/s)	7·51 broad doublet (J_{de} = 11·5 c/s)	9·13 singlet	>8·0 not identified	5·85 quartet (J_{hi} = 7 c/s)	8·72 triplet (J_{hi} = 7 c/s)

TABLE 3. NMR SPECTRUM OF 6-t-BUTYL-9-CARBETHOXY-3-OXODECAHYDROISOQUINOLINE (XV) IN CCl_4 (τ VALUES)

H_a and H_b	H_c	H_d and H_e	H_f	H_g	H_h	H_i
AB quartet at 6·43 τ_a and 6·59 τ_b	1·88 doublet (J = 3 c/s)	AB quartet at 7·51 τ_d and 8·18 τ_e	7·77 Broad singlet	9·13 singlet	5·88 quartet (J_{hi} = 7 c/s)	8·76 triplet (J_{hi} = 7 c/s)

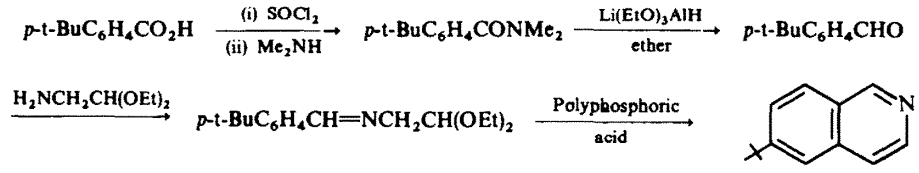
of the fit, however, cannot result in unreserved confidence in the conformation assigned to the heterocyclic ring.



XII

A number of attempts were made at synthesizing the *cis*- and *trans*-6-t-butyldecahydroisoquinolines by the reduction of 6-t-butylisoquinoline (XIII). The latter was prepared in low yield by the Pomeranz-Fritsch cyclization as outlined in Scheme I.

SCHEME I



XIV

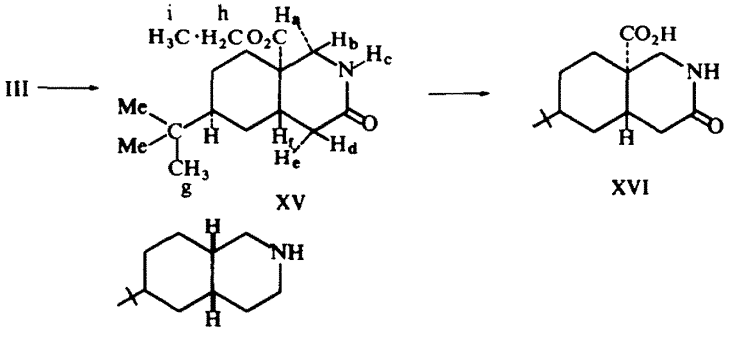
XIII

Various methods were investigated to effect the cyclization XIV → XIII. Treatment of the acetal with hot concentrated sulphuric acid and phosphorus oxychloride[7] or with concentrated H_2SO_4 at $-10°$ and then with H_2SO_4 at 160°[8] gave only tars. When gaseous boron trifluoride was passed through an ethylene chloride solution of XIV[9] the latter was cleaved to p-t-butylbenzaldehyde. Using a modification of Hart's procedure,[10] XIV was heated with polyphosphoric acid at 80–90 to give XIII in a maximum yield of 4%. In view of the low yields of XIII obtained alternative routes to this system were sought. In particular, cyclization of N-*p*-t-butylbenzylaminoacetaldehyde diethyl acetal (obtained by the catalytic reduction of XIV), as described by Vinot[9] for the unsubstituted compound, was attempted with boron trifluoride or with polyphosphoric acid. These reactions only gave unstable oils which appeared to polymerize readily, even when they were dissolved in carbon tetrachloride to determine their NMR spectrum. It would appear as though cyclization had indeed taken place but much more work will be necessary to develop these reactions into preparatively useful methods.

The catalytic reduction of isoquinoline over platinum oxide in acetic and sulphuric acid at room temperature and atmospheric pressure has been reported to give a mixture of *cis*- and *trans*-decahydroisoquinoline in the approximate ratio of 80:20.[11] The crude reduction product of the 6-t-butyl-derivative was incompletely reduced as indicated by the presence of a band at 1620 cm^{-1} in the IR. The mixture could not be resolved by gas chromatography (neither could a synthetic mixture of the *cis*- and *trans*-6-t-butyldecahydroisoquinolines obtained from cyanomalonates I and II) but the retention time of the product was the same as that of VI and XI. A mixture

of picrates was obtained from the catalytic reduction product but due to the small amount of starting material available it could not be resolved adequately into its components. It is important to realize that three fully hydrogenated products are possible in this reduction: the two *cis*-isomers and the *trans*-isomer. In the other *trans*-isomer the t-butyl group would be axial. Gray and Heitmeier[12] have reported that the reduction of isoquinoline with lithium and n-propylamine gave two isomeric octahydroisoquinolines which, when hydrogenated over platinium oxide in acetic acid, gave only *trans*-decahydroisoquinoline. When this sequence was attempted with 6-t-butylisoquinoline very much the same results were obtained as in the direct reduction of XIII and no pure *trans*-isomer could be isolated. Due to the difficulties experienced in obtaining the starting isoquinoline in sufficient amount these studies had to be discontinued for the time being.

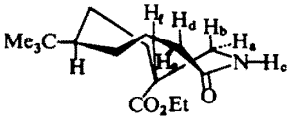
In view of the *trans*-diaxial orientation of the cyano and carbethoxymethyl groups in III it was thought initially that the compound should not undergo reductive cyclization to a lactam readily since this should involve a chair–chair interconversion of the cyclohexane ring, and because of the presence of the t-butyl group which would favour the equatorial conformation ($-\Delta G°_{t\text{-}Bu} > 5$ kcal/mole[13]) the cyclohexane ring would have to adopt a twist-boat conformation in which the t-butyl, cyano and carbethoxymethyl groups would be pseudo-equatorial. Other factors have to be taken into consideration, however. (i) The effective size of C≡N is greatly increased by adsorption at the catalyst surface so that $-\Delta G°$ for the adsorbed cyano group is much greater than 0·15 kcal/mole. This, coupled with the presence of an axial CH_2CO_2H, gives rise to repulsions which will seek relief in the stretched boat conformation. (ii) In addition, once the cyanide has been reduced to aminoethyl ($-\Delta G° >$ 1·7 kcal/mole) the combined diaxial interactions of this and of CH_2CO_2H (>3·4 kcal/mole) would be large enough to reduce appreciably the magnitude of ΔG between the chair and the twist boat forms in equilibrium with each other. Cyclization *via* the latter form would then result in further chair to twist-boat interconversion to restore the equilibrium. In the event, reductive cyclization of III gave 6-t-butyl-9-carbethoxy-3-oxodecahydroisoquinoline (XV) readily. This was saponified to give the stable keto acid (XVI). It was hoped to continue the sequence of decarboxylation and reduction to the *cis*-decahydroisoquinoline (XVII), stereoisomeric with XI. This would have been the first example of the preparation of the two possible isomers



XVIII

of a simple *cis*-decalin type of compound in conformationally pure states. Unfortunately, all attempts to effect the decarboxylation of XVI either gave unchanged starting material or intractable tars.

The NMR spectra of XV measured under various conditions provided confirmation of the twist-boat nature of the cyclohexane ring. The data and assignments are summarized in Table 3. The 1H doublet at 1·88 τ due to the amide NH disappeared on treatment with D_2O. The non-equivalent protons at C_1 gave rise to an AB quartet at 6·43 τ_a and 6·59 τ_b (J_{ab} = 12·5 c/s). Each peak of the A side was a doublet (J_{ac} = 3 c/s) which became a singlet when deuterium oxide was added. Each peak of the B side of the quartet was a singlet, indicating the H_b was not coupled with H_c ($J_{bc} \simeq 0$ c/s). No further splitting is possible since, unlike the situation with VII and IX there is no proton at C_9. A two-proton AB quartet at 7·51 τ_d and 8·18 τ_e (J_{de} = 17 c/s)[14] was attributed to the non-equivalent protons at C_4. On the A side of the quartet each peak was a doublet (J_{df} = 6·5 c/s) and this was unaffected by treating the CCl_4 either with D_2O or with NaOD in D_2O. Proton H_e appeared not to be coupled with H_f ($J_{ef} \simeq 0$ c/s) since each peak of the B side of the quartet was a singlet. The 1H broad unresolved singlet at 7·77 τ was assigned to H_f but this could not be definitely established. The approximate dihedral angles estimated using the modified Karplus curve indicated that the conformation which gave the closest fit was that in which the homocyclic and heterocyclic rings were a twist-boat and half-chair, respectively, as illustrated in XVIII, which is also that which would be expected to arise by reductive cyclization of III.* These results provide an independent proof of the correctness of the geometries assigned to I, II, and III. The carbethoxyl group in XVIII appears to be tucked in below the two rings and shielded from the approach of bulky reagents. This might explain the resistance of XVI to the usual modes of decarboxylation.



XVIII

EXPERIMENTAL

M.ps are uncorrected. IR spectra were recorded on a Perkin–Elmer Model 21 instrument equipped with NaCl optics. NMR spectra were measured on Varian A-60 and HA-100 instruments using TMS as the internal standard.

trans-6-t-Butyl-4-carbethoxy-3-oxodecahydroisoquinoline (IVa)

Diethyl *trans*-4-t-butyl(e)-1-cyano(e)-2-cyclohexylmalonate(e) (II) (4·0 g)[1] in abs EtOH (65 ml) was hydrogenated over Raney Ni (2·0 g) at 115° and an initial press of 1450 psi of H_2 for 8·5 hr. The soln was filtered, the EtOH evaporated and the residual oil (3·390 g, 97%), which crystallized on cooling, was recrystallized from $CHCl_3$–light petroleum (b.p. 40–45°) to give *trans-6-t-butyl-4-carbethoxy-3-oxodecahydroisoquinoline*, m.p. 92·5–93·5°. (Found: C, 68·14, H, 9·64. $C_{16}H_{27}NO_3$ requires: C, 68·29; H, 9·67%.) IR spectrum (KBr disc): 3180 (m), 1733 (s), 1660 (vs), 1390 (w), 1360 (m), 1172 (m), and 840 cm^{-1} (m). The NMR spectral data determined under various conditions are summarized in Table 1.

* The dihedral angles calculated (and those estimated from a Drieding model for a twist-boat, half-chair conformation) were as follows: H_a–H_c 61° or 117° (40°), H_b–H_c 90° (80°), H_d–H_f 44° or 133° (40°), H_e–H_f 90° (80°).

trans-6-*t-Butyl*-3-*oxodecahydroisoquinoline*-4-*carboxylic acid* (IVb)

trans-6-t-Butyl-4-carbethoxy-3-oxodecahydroisoquinoline (1·47 g) was added to a soln of KOH (0·60 g) in water (20 ml) and the stirred mixture was heated to 60° for 6 hr. The cooled soln was filtered, acidified with 5N HCl and the ppt filtered, washed with water and recrystallized from $CHCl_3$–light petroleum (b.p. 40–45°) to give trans-6-*t-butyl*-3-*oxodecahydroisoquinoline*-4-*carboxylic acid* (1·083 g, 82%), m.p. 133–135° with dec). (Found: C, 66·54; H, 9·25. $C_{14}H_{23}NO_3$ requires: C, 66·37; H, 9·15%.) IR spectrum (KBr disc): 3195 (m), 1740 (s), 1655 (vs), 1390 (w), 1360 (m), 1265 (m), 1159 (s), and 1148 cm^{-1} (s).

trans-6-*t-Butyl*-3-*oxodecahydroisoquinoline* (V)

The *trans*-acid (0·82 g) was heated in an oil-bath at 170° until effervescence ceased (5 min) and the residual viscous oil (0·663 g, 98%) was sublimed at 145–155°/10 mm. The white powder was recrystallized from light petroleum (b.p. 60–80°) to give the trans-*lactam*, m.p. 163·5–164·5°. (Found: C, 74·88, H, 11·11. $C_{13}H_{23}NO$ requires: C, 74·59; H, 11·08%). IR spectrum (KBr disc): 3250 (m), 3180 (m), 1670 (s), 1620 (m), 1360 (m), 1232 (w), and 1122cm^{-1} (m).

trans-6-*t-Butyldecahydroisoquinoline* (IV)

trans-6-t-Butyl-3-oxodecahydroisoquinoline (1·0 g) in dry dioxan (30 ml) was added slowly to a suspension of LAH (1·0 g) in dry dioxan (30 ml) and the mixture was boiled under reflux under an atmosphere of dry N_2 for 18 hr. The suspension was cooled, the excess metal hydride was decomposed by the careful addition of water (5 ml), the viscous mixture was extracted with ether (3 × 20 ml) and the combined extracts dried ($MgSO_4$). The solvent was evaporated under reduced press to give trans-6-*t-butyldecahydroisoquinoline* (0·138 g, 14·8%) as a colourless oil, which turned to a white semi-solid (a carbonate or hydrate?) on exposure to air for a short time (20 min). The IR spectrum of the oil (liquid film) had bands at 3280 (w), 1460 (m), 1360 (s), 1140 (m), and 1115 cm^{-1} (m). The semi-solid (KBr disc) had IR bands at 3360 (s), 3280 (m), 2320 (w), 1670 (w), 1615 (m), 1545 (s), 1460 (s), 1420 (s), 1290 (s), 1280 (s), 1250 (s), and 1062 cm^{-1} (w).

The secondary amine was converted into its *picrate* (from EtOH) which, on recrystallization from 85% EtOH, had m.p. 197–198°. (Found: C, 53·93; H, 6·73. $C_{13}H_{25}N$, $C_6H_3N_3O_7$ requires: C, 53·76; H, 6·65%.) IR spectrum (KBr disc): 3235 (m), 1630 (s), 1360 (s), 1332 (s) and 1295 cm^{-1} (s).

cis-6-*t-Butyl*-4-*carbethoxy*-3-*oxodecahydroisoquinoline* (IX)

Diethyl *cis*-4-t-butyl(e)-1-cyano(a)-2-cyclohexylmalonate(e) (0·77 g) was hydrogenated in the same manner as was the *trans*-isomer to give the cis-*ester lactam* (0·585 g, 87·5%), m.p. 138–140° after recrystallization from chloroform–light petroleum (b.p. 40–45°). (Found: C, 68·31; H, 9·39. $C_{16}H_{27}NO_3$ requires: C, 68·29; H, 9·67%.) IR spectrum (KBr disc): 3200 (m), 1732 (s), 1660 (vs), 1365 (m), 1250 (s), and 1038 cm^{-1} (s). The NMR spectra were determined under various conditions and the results are summarized in Table 2.

cis-6-*t-Butyl*-3-*oxodecahydroisoquinoline* (X)

The *cis*-ester lactam (0·167 g) was hydrolyzed in the same way as was the *trans*-isomer to give the crude acid, m.p. 178–179° (0·136 g, 90·5%), which was heated in an oil bath at 195° until effervescence ceased (5 min). The residue (0·108 g, 96·5%) was sublimed at 150–170°/10 mm to give cis-6-*t-butyl*-3-*oxodecahydroisoquinoline*, m.p. 187–188·5° after recrystallization $CHCl_3$–light petroleum (b.p. 60–80°). (Found: C, 74·78; H, 10·91. $C_{13}H_{23}NO$ requires: C, 74·59; H, 11·08%), IR spectrum (KBr disc): 3260 (m), 1650 (s), 1630 (m), 1360 (m), 1325 (s), and 1115 cm^{-1} (m).

cis-6-*t-Butyldecahydroisoquinoline* (XI)

The above *cis*-lactam (0·070 g) was reduced with LAH in the same way as was the *trans*-isomer to give cis-6-*t-butyldecahydroisoquinoline* (0·038 g, 54·4%) as a colourless oil. IR spectrum (liquid film): 3290 (w), 1460 (m), 1360 (s), 1318 (m), 1230 (m), 1138 (m), and 1110 cm^{-1} (w). The *picrate* separated from EtOH and, after recrystallization from 80% EtOH, had m.p. 220–221°. (Found: C, 54·12; H, 6·73. $C_{13}H_{25}N$, $C_6H_3N_3O_7$ requires: C, 53·76; H, 6·65%), IR spectrum (KBr disc): 3100 (m), 1600 (s), 1570 (s), 1360 (s), 1320 (s), 1160 (m), and 1075 cm^{-1} (m).

A mixture of the *cis*- and *trans*-decahydroisoquinolines could not be resolved by GLC or TLC, and a mixture of the corresponding pictates could not be resolved by thin layer chromatography on silica gel.

6-*t-Butyl*-9-*carbethoxy*-3-*oxodecahydroisoquinoline* (XV)

Ethyl 4-t-butyl(e)-2-carbethoxymethyl(a)-1-cyano(a)cyclohexanecarboxylate(e) (III, 1·045 g)[1] in abs

EtOH (24 ml) was hydrogenated over Raney Ni (1 g) at 115° and an initial H_2 press of 1400 psi, for 9 hr. The soln was filtered, the EtOH removed on a steam bath and the remaining viscous oil (0·80 g, 89%) crystallized on treatment with light petroleum (b.p. 40–45°). Recrystallization from CCl_4–light petroleum (b.p. 40–45°) gave *6-t-butyl-9-carbethoxy-3-oxodecahydroisoquinoline*, m.p. 99–100·5°. (Found: C, 68·02; H, 9·59. $C_{16}H_{27}NO_3$ requires: C, 68·29; H, 9·67%). IR spectrum (KBr disc): 3200 (m), 1732 (s), 1658 (vs), 1390 (w), 1362 (m), and 1218 cm^{-1} (s). The NMR spectral data are summarized in Table 3.

6-t-Butyl-3-oxodecahydroisoquinoline-9-carboxylic acid (XVI)

The ester (0·25 g) was stirred at 80° for 4 hr with a soln of KOH (0·224 g) in water (9 ml). The cooled, filtered soln was acidified with 5N HCl and the solid washed with water and dried (0·188 g, 83·5%). An analytical sample was purified by recrystallization from water followed by reprecipitation from basic soln to give *6-t-butyl-3-oxodecahydroisoquinoline-9-carboxylic acid*, m.p. >300°. (Found: C, 66·73; H, 8·95; N, 5·83. $C_{14}H_{23}NO_3$ requires: C, 66·37; H, 9·15; N, 5·53%.) The acid was insoluble in most organic solvents except EtOH. IR spectrum (KBr disc): 3260 (w), 1735 (s), 1655 (vs), 1512 (s), 1372 (m), 1235 (s), and 1127 c,$^{-1}$ (m).

The acid (0·074 g) was heated with $SOCl_2$ (0·5 ml) at 45° for 1·5 hr and the excess $SOCl_2$ removed under vacuum. To the residual oil was added a mixture of abs EtOH (1 ml) and pyridine (1 ml) and the soln was heated at 40–50° for 2 hr. The excess reagents were evaporated *in vacuo*, the residue was diluted with water (2 ml), extracted with ether (3 × 3 ml), and the combined extracts dried ($MgSO_4$). The ether was distilled and the residue (0·069 g, 84%) was recrystallized from CCl_4–light petroleum (b.p. 40–45°) to give the ester, m.p. 98–100°, identical in all respects with 6-t-butyl-9-carbethoxy-3-oxodecahydroisoquinoline.

Attempted decarboxylation of 6-t-butyl-3-oxodecahydroisoquinoline-9-carboxylic acid

(a) *Thermally.* The acid (5 mg) was heated to 335° (it melted at ca. 325–330°) for 5 min, but no gas evolution was observed and, on cooling, the unchanged acid was recovered.

(b) *With dilute hydrochloric acid.* The acid (25 mg) in 2N HCl (6 ml) was boiled under reflux for 56 hr, the soln cooled and the recovered solid washed and dried. It proved to be identical with the starting acid.

(c) *With collidine.* The acid was recovered unchanged after boiling under reflux with collidine for 1·5 hr.

(d) *With copper and quinoline.* Freshly precipitated Cu powder (5 mg) was added to a soln of the acid (12 mg) in quinoline (0·4 g) and the mixture was boiled under reflux for 1 hr. The cooled soln was filtered and evaporated to dryness to give a black viscous tar (6 mg). IR spectrum: 2940 (m), 2850 (m), 2300 (w), 1785 (m), 1710–1590 (m), 1360 (w), 1000 (w), and 800 cm^{-1} (m). This tar was dissolved in ether and injected into a gas chromatograph using a 3 ft. × ¼ in. column packed with Apiezon M (20% w/w) on Gas-Chrom P (60–80 mesh) at 210° (injector temp 240°) and a He flow rate of 100 ml/min. No decarboxylated product could be detected. Under these conditions, *trans*-6-t-butyl-3-oxodecahydroisoquinoline had a retention time of 16 min.

Similarly, no decarboxylated product could be isolated from the reaction of the acid with lead tetracetate and iodine followed by hydrogenation,[15] or by heating the acid with soda-lime at 325–335° for 20 min. In both cases, tars or brown glasses were obtained which could not be purified by GLC.

N,N-*Dimethyl*-p-*t-butylbenzamide*

Thionyl chloride (10·2 ml) was added slowly to *p*-t-butylbenzoic acid (10·0 g), the mixture was heated to 95° for 3 hr and the excess $SOCl_2$ was removed under reduced press. The crude *p*-t-butylbenzoyl chloride (11·0 g) was poured slowly into a stirred soln of 25% aqueous Me_2NH (11·0 g) in 10% NaOH aq (28 ml) and the temp maintained at 0–10° for 20 min. The ppt was washed with water and recrystallized from MeOH–light petroleum (b.p. 40–45°) to give N,N-*dimethyl*-p-*t-butylbenzamide*, m.p. 88–89°. (Found: C, 76·02; H, 9·40. $C_{13}H_{19}NO$ requires: C, 76·05; H, 9·33%.) IR spectrum (KBr disc): 1630 (s), 1370 (s), 1273 (m), 1118 (m), 855 (m), 837 (m), 770 (m), and 712 cm^{-1} (m); NMR spectrum (CCl_4) τ: 2·73 (4H singlet); 7·04 (6H singlet); 8·7 (9H singlet).

p-*t-butylbenzaldehyde*

A 1·1M LAH soln in dry ether (87·3 ml, 0·096 moles) at 0° was treated dropwise with AcOEt (12·7 ml, 0·144 moles; dried over CaH_2) at such a rate that the temp was maintained at 0° while stirring under a N_2 atm. A soln of N,N-dimethyl-*p*-t-butylbenzamide (26·4 g, 0·08 moles) in dry ether (200 ml) was then added dropwise at 0° and the mixture was stirred for a further 2 hr. It was then treated with ice-cold 5N H_2SO_4, the organic layer was separated and the aqueous phase was extracted with ether (3 × 10 ml).

The combined organic layers were dried ($MgSO_4$), the solvent evaporated and the residue distilled to give *p*-t-butylbenzaldehyde, b.p. 123–126°/15 mm (7·6 g, 61%). The 2,4-dinitrophenylhydrazone had m.p. 250–252°. Wender *et al.*[16] give b.p. 130°/25 mm for the aldehyde and m.p. 249–251° for the 2,4-dinitrophenylhydrazone. The NMR spectrum of the aldehyde (in CCl_4) was as follows, τ: 0·18 (1H singlet); 2·43 (4H quartet J = 8·5 c/s, each peak a triplet, J = 1·5 c/s); 8·69 (9H singlet).

N-p-*t-Butylbenzylidenaminoacetaldehyde diethyl acetal* (XIV)

A mixture of *p*-t-butylbenzaldehyde (11·83 g) and aminoacetaldehyde diethyl acetal (10·12 g) was heated on a steam-bath for 2 hr, cooled, and the aqueous layer siphoned off. Distillation of the residual oil gave N-p-*t-butylbenzylidenaminoacetaldehyde diethyl acetal*, b.p. 106°/0·1 mm (17·4 g, 86·5%.) (Found: C, 73·21; H, 9·39. $C_{17}H_{27}NO_2$ requires: C, 73·60; H, 9·81%.) IR spectrum (liquid film): 1652 (m), 1620 (w), 1575 (w), 1372 (m), 1130 (s), 1070 (s), 1020 (s), and 830 cm^{-1} (m), λ_{max} (95% EtOH): 258, 289 mμ; $\varepsilon \times 10^{-3}$ 21·2, 1·8; NMR spectrum (CCl_4) τ: 1·89 (1H, triplet, J = 1 c/s); AB quartet at 2·43 τ_A and 2·7 τ_B (4H, J_{AB} = 9 c/s; each peak a triplet, $J_{AA'} = J_{BB'}$ = 2 c/s); 5·31 (1H triplet, J = 5·2 c/s); 6·2–6·8 (6H multiplet); 8·7 (9H singlet); 8·86 (6H, triplet J = 7 c/s).

N-p-*t-Butylbenzylaminoacetaldehyde diethyl acetyl*

The benzylidene acetal (3·05 g) in 95% EtOH (40 ml) was hydrogenated over 10% Pd–C (0·14 g) at room temp and atm press until absorption of H_2 ceased (2·5 hr). The soln was filtered, the EtOH evaporated and the residual oil distilled to give the *benzylamino acetal*, b.p. 94–95°/0·07 mm (2·31 g, 68·5%). (Found: C, 73·29, H, 10·42. $C_{17}H_{29}NO_2$ requires: C, 73·07; H, 10·46%). IR spectrum (liquid film): 3330 (vw), 1510 (w), 1360 (m), 1125 (s), 1058 (s), 1015 (m), and 850 cm^{-1} (w); NMR spectrum (CCl_4), τ: 2·83 (4H singlet); 5·51 (1H triplet, J = 5·5 c/s); 6·33 (2H singlet); 6·38 to 6·8 (4H multiplet); 7·39 (2H doublet, J = 5·5 c/s); 8·6 (1H singlet, removed by exchange with D_2O); 8·71 (9H singlet); 8·88 (6H triplet, J = 7 c/s).

6-*t-Butylisoquinoline* (XIII)

N-*p*-t-Butylbenzylideneaminoacetaldehyde diethyl acetal (2·0 g) was added to a stirred soln of polyphosphoric acid [from P_2O_5 (30·0 g), added slowly (2 hr) to 85% orthophosphoric acid (30·0 g) with stirring; $POCl_3$ (2 ml) was added just prior to the addition of the amino acetal] and the mixture was heated at 87–97° for 2 hr. The viscous product was poured into ice-water (50 ml) and extracted with ether (3 × 20 ml). The aqueous phase was made strongly basic with 20% NaOH aq (200 ml), saturated with salt and extracted with ether (5 × 15 ml), and the combined extracts dried (KOH). Evaporation of the solvent gave a reddish brown oil which partly crystallized on cooling. Sublimation at 80–90°/15 mm gave 6-*t-butylisoquinoline*, m.p. 55–56° (0·054 g, 4·04%). (Found: C, 84·65; H, 8·03. $C_{13}H_{15}N$ requires: C, 84·28; H, 8·16%). IR spectrum (KBr disc): 1635 (s), 1592 (m), 1380 (s), 1288 (s), 1255 (w), 955 (s), 895 (s), 833 (vs), and 675 cm^{-1} (s).

The *picrate* separated from EtOH and, after recrystallization from benzene–light petroleum (b.p. 40–45°) had m.p. 194·5–195·5°. (Found: C, 55·18; H, 4·53. $C_{13}H_{15}N$, $C_6H_3N_3O_7$ requires: C, 55·07; H, 4·38%.)

Attempted preparation of authentic cis-6-*t-butyldecahydroisoquinoline* (cf. Witkop[11])

6-t-Butylisoquinoline (0·20 g) in glacial AcOH (3 ml) and conc H_2SO_4 (5 drops) was hydrogenated over PtO_2 (0·20 g) at room temp and 41 psi of H_2 for 24 hr. The soln was filtered, made basic with 20% NaOH aq, extracted with ether (5 × 10 ml), and the combined extracts were dried ($MgSO_4$). The solvent was evaporated to give an oil (0·151 g) which gave only a single peak when analyzed by GLC on a number of columns. The retention times were the same as those of *cis*- and of *trans*-decahydroisoquinoline. IR spectrum (liquid film): 3280 (m), 1730 (w), 1620 (m), 1550 (m), 1360 (s), 1260 (m), 1230 (m), 835 (w), 800 (w) and 735 cm^{-1} (w). The oil was converted into a mixture of picrates (from 95% EtOH) which was fractionally crystallized from 80% EtOH. Two fractions were obtained, m.p. 198–205° and 230–238°, respectively. These could not be purified any further and neither could the mixture of picrates be resolved by thin layer chromatography on silica gel.

Attempted preparation of authentic trans-6-*t-butyldecahydroisoquinoline* (cf. Gray and Heitmeier[12])

A mixture of 6-t-butylisoquinoline (0·20 g), finely cut pieces of Li metal (0·12 g) and n-propylamine (5 ml) was stirred at room temp under dry N_2. Within 1 hr the reaction mixture turned from colourless to blood-red to green. It was then boiled under reflux for 6 hr and kept at just below reflux temp for another 12 hr. The excess Li metal was removed and the mixture was heated with solid NH_4Cl and then with water (10 ml).

It was then extracted with ether (5 × 10 ml) and the combined extracts dried ($MgSO_4$). The crude oil contained 10% of unreacted 6-t-butylisoquinoline as shown by GLC on a 2 ft × ¼ in. solumn packed with Apiezon M (25% w/w) on Chromosorb W (60–80 mesh) at 190° and a He inlet press of 30 psi. Under these conditions 6-t-butylisoquinoline had a retention time of 12 min while the partially reduced product had a retention time of 7·5 min. The reaction was repeated using Li (0·01 g) in n-propylamine (5 ml), and the reaction temp was maintained at 40° for 16 hr. The crude product (0·12 g) was shown by GLC to contain only the partially reduced compound. IR spectrum (liquid film): 3270 (w), 1730 (w), 1645 (m), 1360 (m), 1250 (m), 1140 (w), 1080 (w), 835 (w), 800 (w) and 750 cm^{-1} (w). It was distilled at 58–64°/0·4 mm, and the distillate (0·090 g) in glacial AcOH (5 ml) was hydrogenated over PtO_2 (0·150 g) at room temp and a H_2 press of 46 psi for 10 days. The suspension was filtered and worked up as before to give an oil (0·06 g) which gave a single peak on GLC on a variety of columns. IR spectrum (liquid film): 3270 (w), 1610 (w), 1530 (w), 1360 (s), 1258 (m), 1230 (w), 1110 (w), 1080 (w), 838 (w), 798 (s) and 740 cm^{-1} (w). It, too, gave a mixture of picrates from 95% EtOH which, on fractional crystallization from 80% EtOH, gave two fractions, m.p. 178–210° and 230–235°. Unfortunately, these could not be purified further.

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