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1,2-DIHYDROISOQUINOLINES—III

DIMERIZATION

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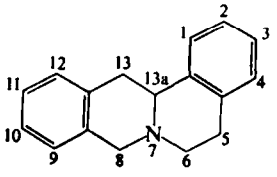
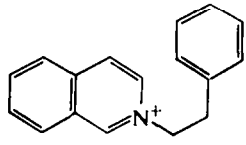
Abstract—Treatment of N-β-phenylethylisoquinolinium bromide (II) with strong alkali followed by strong acid gives N-β-phenylethylisocarbostyril (III) and a dimer formulated as (X). The method described by Grewe *et al.*[4] for the preparation of 4-alkyl or 4-arylalkylisoquinoline derivatives has been shown to yield the corresponding N-substituted isoquinolines.

IN PART II[1] it was shown that good yields of berbine (I) derivatives could be obtained by treating N-β-arylethylisoquinolinium salts with strong alkali, followed by strong mineral acid. It was found that the N-β-arylethylisocarbostyrils produced in the alkaline disproportionation reaction, as well as the N-β-arylethyl-1,2-dihydroisoquinolines, underwent ring closure upon treatment with mineral acid; a number of isoquinolinium salts containing methoxyl substituents at various positions were studied and successfully ring-closed.

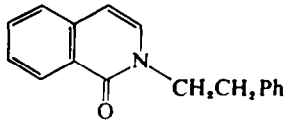
When N-β-phenylethylisoquinolinium bromide (II) itself was treated successively with conc. aqueous alkali and conc. hydrochloric acid, under the conditions described previously,[1] the isocarbostyril (III) was isolated (in 27% yield, based upon (II)), from



I



II



III

the non-basic fraction of the reaction mixture. It was always recovered unchanged in other, separate attempts to cyclize it under acidic conditions. The basic fraction of the reaction mixture gave a "compound A" (29% yield), isolated as the hydrochloride, m.p. 252–253°. This substance analysed for $(C_{17}H_{18}NCl)_n$; its UV absorption was similar to that of a 1,2-dihydroisoquinoline and bands at 2700–2400 cm^{-1} and 1640 cm^{-1} in the IR indicated the presence of $\rightarrow\overset{+}{N}H$ and $>C{=}C<$ groups respectively. Since compound A was not very stable it was reduced either catalytically, or with sodium borohydride to a dihydro derivative, hydrochloride m.p. 254–256°. The UV spectrum of this material corresponded to benzenoid absorption only. Specimens of

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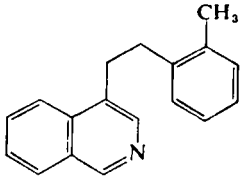
[1] D. W. Brown and S. F. Dyke, *Tetrahedron* **22**, 2429 (1966).

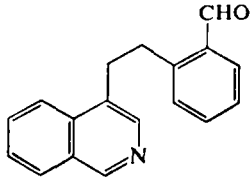
berbine[2] (I) and 2-β-phenylethyl-1,2,3,4-tetrahydroisoquinoline were prepared and shown to be different from dihydro-A. The reported physical constants of 1-β-phenylethyl[3] and of 3-β-phenylethylisoquinoline[3] were different from those observed for the dehydrogenation products of the unknown compound. Dihydro-A was also shown to be different from a compound described[4] as 4-β-phenylethyl-1,2,3,4-tetrahydroisoquinoline[5] (but see below).

Repeated analyses of dihydro-A and its derivatives gave a result a little low in carbon for $C_{17}H_{20}NCl$, and mol. wt. determinations in camphor and in cyclohexanol indicated a monomeric structure. However, the degradations outlined below show clearly that dihydro-A must be dimeric.

When the compound dihydro-A was heated with Pd-black at 210° a strong odour of ammonia was detected, and a 70% yield of ethylbenzene was collected. The dark residue was chromatographed over silica gel and two crystalline solids were isolated. The first fraction, m.p. 65–68° analysed for $C_{18}H_{17}N$; the UV absorption was typically that of an isoquinoline structure, and the IR spectrum suggested the presence of >C=N— (band at 1620 cm^{-1}). The NMR spectrum (in $CDCl_3$ with chemical shifts shown in ppm from TMS as an internal reference) was diagnostic for the structure (IV) (Fig. I). The second product of the dehydrogenation of dihydro-A, m.p. 104° was shown by a similar combination of physical methods to be the corresponding aldehyde (V). A third fraction could not be obtained analytically pure, but it has been



IV



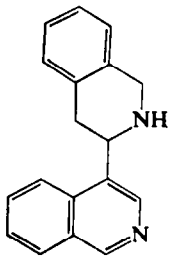
V

tentatively identified, mainly through its NMR spectrum, to be the dimer (VI). A similar dimeric product (VIII) has been reported[6] as a by-product in the ring-closure of the reduced amino-acetal (VII), presumably via the 1,2-dihydroisoquinoline.

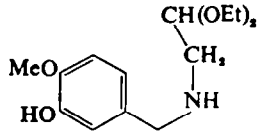
The above evidence indicates that compound dihydro-A has structure (XI) and that compound A itself is (X), formed from (IX) as shown. It is thought that the three products of dehydrogenation of (XI) arise as indicated in (XI) → (XII) → (V) → (IV).

Confirmation of structure XI was sought by the unambiguous synthesis of IV. The most direct route appeared to be that due to Grewe *et al.*[4] in which 4-β-phenylethyl-1,2,3,4-tetrahydroisoquinoline (XV R = H) was reported to be formed when a mixture of isoquinoline and phenylacetaldehyde was catalytically reduced in acetic acid solution. Presumably[4] the initially formed 1,2-dihydroisoquinoline (XIII) condenses with the aldehyde to yield XIV and this is then reduced to XV. This

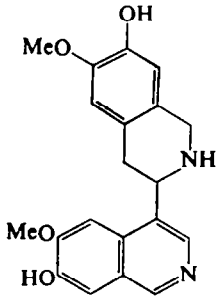
[2] S. Chakravarti, R. D. Haworth and W. H. Perkin, *J. Chem. Soc.* 2278 (1927); W. Leithe, *Ber. Dtsch. Chem. Ges* **63**, 2343 (1930).
[3] M. Avramoff and Y. Sprinzak, *J. Amer. Chem. Soc.* **78**, 4096 (1956).
[4] R. Grewe, W. Kruger and E. Vangermain, *Chem. Ber.* **97**, 119 (1964).
[5] We are indebted to Professor Grewe for a sample of this compound.
[6] J. M. Bobbit, J. M. Kiely, K. L. Khana and R. Ebermann, *J. Org. Chem.* **30**, 2247 (1965).



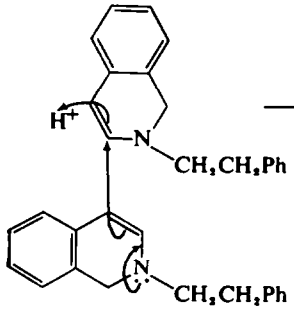
VI



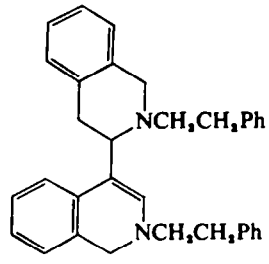
VII



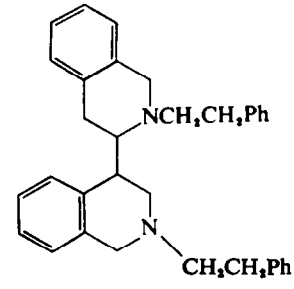
VII I



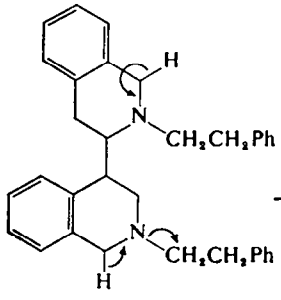
IX



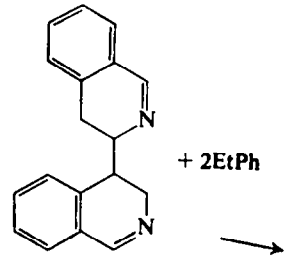
X



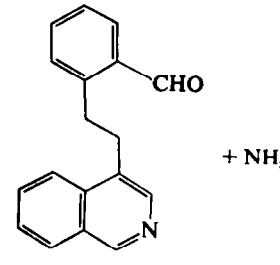
XI



XI



XII



V

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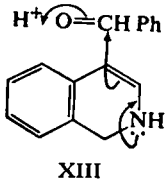
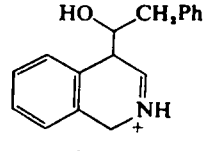
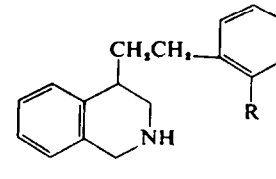


XIII



XIV



XV

reaction was repeated using *o*-methylphenylacetaldehyde and isoquinoline, and the product analysed correctly for the expected 4-*β*-(*o*-methylphenyl)ethyl-1,2,3,4-tetrahydroisoquinoline (XV, R = Me). However, dehydrogenation with Pd–black gave isoquinoline itself as the only basic product, with no trace of the expected IV. Further examination of the products of the reductive condensation of isoquinoline with *o*-methylphenylacetaldehyde, and with phenylacetaldehyde revealed that they are the N-*β*-arylethyltetrahydroisoquinolines.

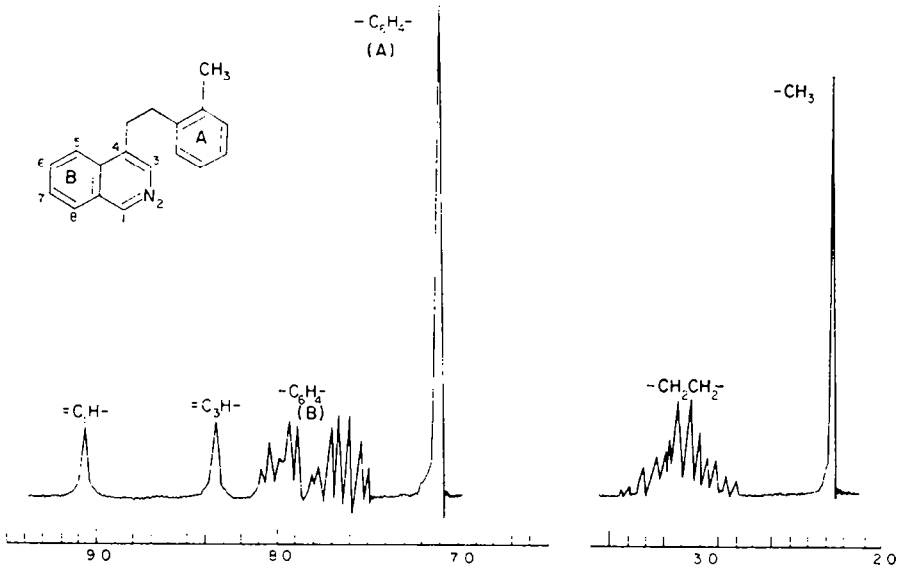


FIG. I. The NMR spectrum of 4-(*o*-methylphenyl)ethylisoquinoline.

Since structure XV (R = H) was allocated[4] by analogy with the product from isoquinoline and benzaldehyde, this reaction was repeated using the published[4] procedure. Grewe *et al.* reported the production, and separation by fractional distillation of three basic compounds. One was identified as 4-benzylisoquinoline by comparison with an authentic specimen,[7] and since the major component (hydrochloride m.p. 202°) gave 4-benzylisoquinoline when dehydrogenated, it was assumed to be 4-benzyl-1,2,3,4-tetrahydroisoquinoline. The third compound, m.p. 89°, was allocated the structure of 4,4-dibenzyl-1,2,3,4-tetrahydroisoquinoline. A similar C_4-benzylation of a 1,2-dihydroisoquinoline has been described by Bobbitt *et al.*[8] 4-Benzylisoquinoline has also been obtained[9] (in 34% yield) by heating together a mixture of 1,2,3,4-tetrahydroisoquinoline and benzaldehyde in acetic acid; a 1,2-dihydroisoquinoline intermediate was proposed to participate in this reaction.

In our hands the reductive condensation of isoquinoline with benzaldehyde yielded, after chromatography over silica gel, 4-benzylisoquinoline (13%) m.p. 118–119°, whose structure was confirmed by its NMR spectrum (Fig. II), an oily base

[7] J. Braun, O. Bayer and L. Cassel, *Ber. Dtsch. Chem. Ges.* **60**, 2602 (1927).
[8] J. M. Bobbitt, D. P. Winter and J. M. Kiely, *J. Org. Chem.* **30**, 2459 (1965).
[9] W. D. Burrows and E. P. Burrows, *J. Org. Chem.* **28**, 1180 (1963).

(10%), hydrochloride m.p. 202° and a crystalline base (11%) m.p. 89°. The oily base was quickly shown, by reduction of N-benzylisoquinolinium bromide with sodium borohydride and comparison of samples, to be 2-benzyl-1,2,3,4-tetrahydroisoquinoline and not the 4-benzyl compound as claimed by Grewe. The analysis of the methiodide of our base, m.p. 89°, suggested that the compound is more correctly formulated as 2,4-dibenzyl-1,2,3,4-tetrahydroisoquinoline. No 4-benzyl-1,2,3,4-tetrahydroisoquinoline was detected in our reaction. The possibility of a benzyl migration from nitrogen to C_4 during dehydrogenation of N-benzyl-1,2,3,4-tetrahydroisoquinoline was discounted when it was found that our compound gave only isoquinoline and toluene

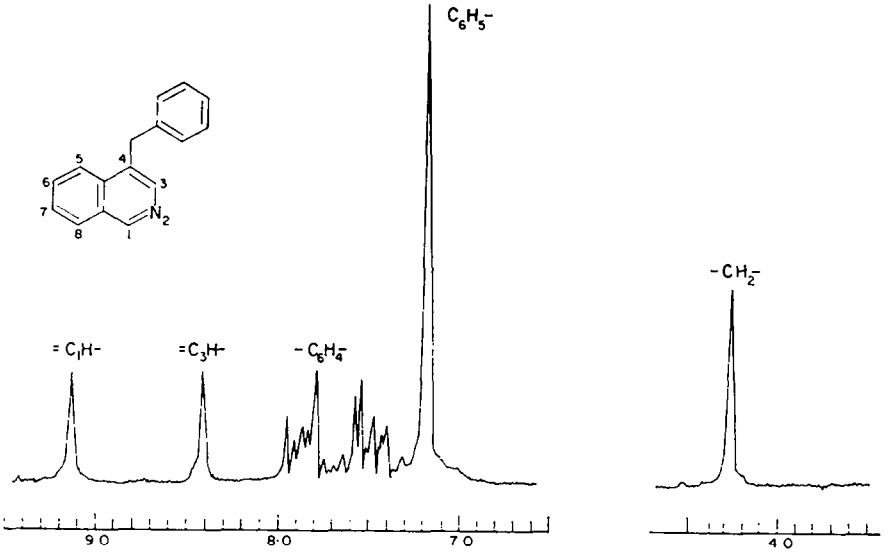


FIG. II. The NMR spectrum of 4-benzylisoquinoline.

when it was heated with Pd. The compound described by Grewe as 4-cyclohexyl-1,2,3,4-tetrahydroisoquinoline, and obtained by reductive condensation of isoquinoline and cyclohexanone, has been found, by elemental analysis of its methiodide, to be the 2-cyclohexyltetrahydroisoquinoline.

EXPERIMENTAL

M.ps are not corrected.

N-*β-Phenylethylisoquinolinium bromide* (II). A mixture of isoquinoline (30·0 g) and β-phenylethyl bromide (45·0 g) was warmed to 90°; the temp then rose rapidly to 185° as the exothermic reaction commenced. The brown liquid was cooled to 120° then poured slowly into stirred EtOH (50 ml). The off-white solid (70 g) was collected, m.p. 151–152° and recrystallized from EtOH, m.p. 152–153°. (Found: C, 64·5; H, 5·4; N, 4·3; Br, 25·2. $C_{17}H_{16}NBr$ requires: C, 65·0; H, 5·1; N, 4·5; Br, 25·4%.) A compound described as II has been reported in the literature,[10] but a m.p. 72·7–73·9° was reported and the analysis required 4/3 moles water.

N-*β-Phenylethylisocarbostyril* (III). N-β-Phenylethylisoquinolinium iodide (12·0 g) was dissolved in 50% aqueous EtOH (40 ml) and treated with KOH (5·0 g) and $K_3Fe(CN)_6$ (14·0 g) in water (30 ml). After heating on the waterbath for 30 min, the liquid was cooled and extracted with ether. The ethereal solution was dried and evaporated to yield light brown crystals (5·0 g) m.p. 97–98°. Recrystallization from EtOH gave III, m.p. 98°. (Found: C, 82·05; H, 6·1; N, 5·9; $C_{17}H_{15}NO$ requires: C, 81·9; H, 6·1; N, 5·6%.)

[10] J. Hartwell and S. Kornberg, *J. Amer. Chem. Soc.* **68**, 868 (1946).

N-β-Phenylethyl-1,2,3,4-tetrahydroisoquinoline. A solution of N-β-phenylethylisoquinolinium iodide (1·0 g) in 20% aqueous EtOH (50 ml) was treated with $NaBH_4$ (0·3 g). After heating on the waterbath for 1 hr, the solution was poured into water (300 ml) and extracted with ether. A colourless oil was recovered from the ether, which gave the hydrochloride of N-β-phenylethyl-1,2,3,4-tetrahydro-isoquinoline as white needles, m.p. 227–228°. When crystallized from EtOH (Lit.[11] m.p. 227°). (Found: C, 74·8; H, 7·2; N, 4·9. Calc. for $C_{17}H_{20}NCl$: C, 74·6; H, 7·3; N, 5·1%.)

The dimerization reaction. A solution of II (70 g) in aqueous EtOH (80 ml) was poured into 33% NaOHaq (300 ml) contained in a separating funnel. The resultant red oil was run into conc HCl 150 ml) and the mixture was left overnight. The resultant solid cake was collected and sucked dry, and then triturated with acetone. The residual solid (17·5 g), m.p. 248–252° was recrystallized from MeOH to yield "*Compound A*", hydrochloride m.p. 254–255° as white needles. (Found: C, 73·2; H, 6·7; N, 4·9; Cl, 13·35. $C_{34}H_{36}N_2Cl_2$ requires: C, 75·1; H, 6·6; N, 5·2; Cl, 13·1%.)

Compound III, m.p. 96–97° (15·0 g) was recovered from the acetone solution.

Compound A from III. The isocarbostyril (12·5 g) was suspended in anhydrous ether (250 ml) and LAH (2·5 g) was added during 30 min. After leaving the reaction mixture overnight, it was decomposed and the red oily base (in some runs a yellow solid m.p. 65–67°, rapidly becoming red was formed) was dissolved in conc HCl (60 ml) and the solution was allowed to stand overnight. After dilution with water and basification with ammonia the base was collected and characterized as its hydrochloride, m.p. 254–255° (6·0 g).

Reduction of compound A to dihydro-A. A solution of compound A hydrochloride (10·0 g) in warm MeOH (50 ml) was treated with $NaBH_4$ (2·0 g), and the mixture heated under reflux for 20 min. The dihydro-A, hydrochloride m.p. 256–257° was obtained from water containing 1 drop conc HCl (7·5 g). (Found: C, 73·7; H, 7·2; N, 4·9; Cl, 13·05. $C_{34}H_{38}N_2Cl_2$ requires: C, 74·9; H, 7·0; N, 5·1; Cl, 13·0%.)

Dehydrogenation of dihydro-A. The base derived from 5·5 g of dihydro-A hydrochloride was heated to 205° with Pd-black (0·5 g) for 1½ hr. Ethylbenzene (1·5 g) was collected as a distillate, b.p. 135°. A strong odour of ammonia was detected. After cooling acetone was added to the residue in the flask, and the mixture was filtered to remove Pd. The acetone was evaporated to leave a mixture of bases (2·6 g) which was separated by chromatography over silica gel. Elution with a 25% AcOEt in petrol (60–80°) gave firstly 4-β-(*o*-methylphenyl)ethylisoquinoline (0·8 g), m.p. 65–67°. The *methiodide* was obtained from EtOH, m.p. 176°. (Found: C, 58·6; H, 5·3; N, 3·3; I, 32·5. $C_{19}H_{20}NI$ requires: C, 58·6; H, 5·2; N, 3·6; I, 32·6%.) The second fraction from the column (0·15 g) was *o*-[4-β-phenylethylisoquinolyl]benzaldehyde, m.p. 98–101°. The *methiodide* was crystallized from EtOH, m.p. 205–206°. (Found: C, 56·6; H, 4·5; N, 3·3. $C_{19}H_{18}NIO$ requires: C, 56·6; H, 4·5; N, 3·5%.) Finally, elution of the column with 50% AcOEt in petrol (60–80°) yielded a brown oil (1·0 g) which could not be obtained analytically pure.

N-Benzylisoquinolinium bromide. Equimolecular quantities of isoquinoline and benzyl bromide were heated together for 2 hr on a steam bath. The crystalline solid was recrystallized from EtOH to give a 90% yield of the quaternary salt, m.p. 110–112° (Lit.[12] m.p. 110–111·5°.)

N-Benzyl-1,2,3,4-tetrahydroisoquinoline. A solution of the above quaternary bromide (4·0 g) in EtOH (30 ml) and water (15 ml) was treated with $NaHB_4$ (1·0 g) and the mixture was heated on a steam bath for 1 hr. Water was added and the mixture was extracted with ether. The colourless oily base was converted to its hydrochloride (3·0 g). Recrystallization from EtOH gave a white solid, m.p. 201–202°. (Found: C, 74·2; H, 7·0; N, 5·2; Cl, 13·5. $C_{16}H_{18}NCl$ requires: C, 74·0; H, 7·0; N, 5·4; Cl, 13·7%.)

Reductive alkylation of isoquinoline with benzaldehyde. To a solution of isoquinoline (2·54 g) and benzaldehyde (2·6 g) in AcOH (15 ml) was added PtO_2 (50 mg), and the mixture was shaken with H_2 at room temp and 2 atm press for 18 hr. The filtrate from the catalyst was poured into 2N HCl and then extracted with ether. The ether extract was discarded, and the acid aqueous solution was made alkaline with ammonia and extracted with ether. An oil (3·5 g) was recovered from the ethereal solution and this was chromatographed over silica gel (70 g). Elution with 25% AcOEt in petrol (60–80°) gave firstly a solid (0·7 g) m.p. 83–86°. Recrystallization from EtOH raised this to m.p. 90°.

[11] R. D. Haworth, W. H. Perkin and H. S. Pink, *J. Chem. Soc.* 1716 (1925).
[12] F. Krönke, *Ber. Dtsch. Chem. Ges.* **68**, 1351 (1935).

The methiodide was obtained from EtOH m.p. 201–202°. (Found: C, 63·1; H, 5·4; N, 3·0; I, 28·45; NCH_3, 6·5. 4,4-Dibenzyl-1,2,3,4-tetrahydroisoquinoline methiodide requires: C, 64·0; H, 6·0; N, 3·0; I, 27·0; NCH_3 12·7%. 2,4-Dibenzyl-1,2,3,4-tetrahydroisoquinoline methiodide requires: C, 63·3; H, 5·75; N, 3·1; I, 27·9; NCH_3, 6·4%.) The second fraction from the column (0·5 g) was characterized as N-benzyl-1,2,3,4-tetrahydroisoquinoline hydrochloride from EtOH, m.p. 199–202°, undepressed by the material obtained above by reduction of N-benzylisoquinolinium bromide. Fraction 3 (0·55 g), m.p. 116–118°, proved to be 4-benzylisoquinoline. The next fraction was isoquinoline (0·70 g), methiodide m.p. 159° and the final product (0·05 g), m.p. 221–223°, is a crystalline base of unknown structure.

Dehydrogenation of N-*benzyl*-1,2,3,4-*tetrahydroisoquinoline.* The base (0·35 g) from the hydrochloride m.p. 202°, obtained in the reductive condensation reaction described above, was dissolved in decalin (2·5 ml) and heated at 195–205° for 1½ hr with 10% Pd–C (0·2 g). The filtrate from the catalyst was worked up in the usual way for basic material. Isoquinoline (0·15 g; 75%) and toluene (0·08 g; 65%) were obtained and identified by their IR spectra.

Similar results were obtained by the use of Pd–black.

o-Tolylacetaldehyde. Phosphorus pentachloride (35 g) was added to *o*-tolylacetic acid (25 g) and after the vigorous reaction had subsided, the mixture was heated on the waterbath for 35 min. $POCl_3$ was removed under reduced press and *o*-tolylacetyl chloride distilled as a colourless liquid (23·5 g) b.p. 69–70/0·3 mm. A mixture of *o*-xylene (100 ml), the acid chloride (22·0 g) and 5% Pd on $BaSO_4$ (2·4 g) was heated under reflux whilst the Rosenmund reduction[18] was carried out. *o*-Tolylacetaldehyde (10 g) was collected as a pale yellow oil b.p. 72–75°/5mm.

Reductive alkylation of isoquinoline with o-tolylacetaldehyde. A mixture of isoquinoline (2·54 g), the above aldehyde (3·2 g), AcOH (30 ml) and PtO_2 (50 mg) was hydrogenated at room temp and 45 lb per sq in. press for 16 hr. The reaction mixture was worked up as described for the benzylation reaction above and an oil (2·0 g) was collected. Treatment of this with acetone and a few drops conc HCl gave a white solid (1·0 g) m.p. 212–215°. Repeated recrystallization from EtOH gave white needles of N-β-(*o*-methylphenyl)-ethyl-1,2,3,4-tetrahydroisoquinoline m.p. 216–217°. (Found: C, 75·1; H, 7·8; N, 4·5; Cl, 12·1. $C_{18}H_{22}NCl$ requires: C, 75·1; H, 7·65; N, 4·9; Cl, 12·3%.) Attempted dehydrogenation with Pd black at 290° yielded isoquinoline as the only basic product.

Reductive alkylation of isoquinoline with phenylacetaldehyde. A mixture of isoquinoline (2·3 g), phenylacetaldehyde (2·6 g), AcOH (20 ml) and PtO_2 (50 mg) was shaken with H_2 at 2 atm press for 24 hr. The base, was characterized as N-β-phenylethyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (1·0 g) m.p. 227–228°, undepressed upon admixture with the sample prepared as described above.

Reductive alkylation of isoquinoline with cyclohexanone. Using an exactly similar procedure to that described above a white hydrochloride salt (51% yield based on isoquinoline), m.p. 226–227° from ether–acetone was produced. (Found: C, 71·25; H, 9·2; N, 5·55; Cl, 13·9. $C_{15}H_{22}NCl$ requires: C, 71·5; H, 8·8; N, 5·6; Cl, 14·1%.) The methiodide was crystallized from EtOH m.p. 219–219·5°. (Found: C, 53·6; H, 6·5; N, 3·7; I, 35·2; NCH_3, 8·2. The methiodide of 4-cyclohexyl-1,2,3,4-tetrahydroisoquinoline requires: C, 55·1; H, 7·1; N, 3·8; I, 34·3% whereas the methiodide of N-cyclohexyl-1,2,3,4-tetrahydroisoquinoline requires: C, 53·8; H, 6·8; N, 3·9; I, 35·5; NCH_3, 8·1%.)

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[18] E. B. Herschberg and J. Cason, *Organic Synthesis* Coll. Volume III; p. 627. Wiley, New York (1955).