218. *The Octahydropyridocoline–Norlupinane Relationship. Part II.*

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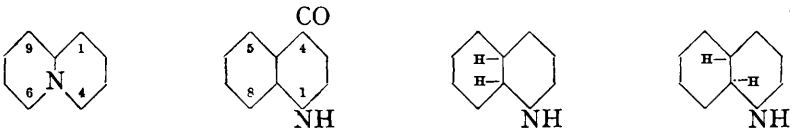
In continuation of our study of the isomerism of the octahydropyridocolines, we have synthesised *4-ketodecahydroquinoline* in the hope that its reduction by the Clemmensen and the Wolff method would afford a crucial test of the hypothesis that the octahydropyridocolines are *cis-trans* isomers. Unfortunately, both reduction methods give *trans*-decahydroquinoline, the test breaking down when it was found that the *cis*- was converted into the *trans*-form by boiling with hydrochloric acid.

In addition the reduction of *1-keto-8-methyloctahydropyridocoline* has been investigated and found to give A and B *forms* of methyloctahydropyridocoline which are not interconvertible by hydrochloric acid and sodium ethoxide respectively.

The steric stability of the octahydropyridocolines is thus much greater than that of the decahydroquinolines.

The production of two forms of octahydropyridocoline B and A (I) by the reduction of 1-keto-octahydropyridocoline by the Clemmensen and the Wolff method respectively [J., 1931, 437; 1936, 1429 (Part I of this series)] has been explained by their being geometrical isomers of the *cis-trans*-decalin type. As a direct proof of such isomerism has not been possible and one or two experimental facts do not readily fit in with this view, such as the absence of 1-methyl-2-*n*-butylpiperidine from the reduction products of the substances obtained by the Hofmann degradation of the base B, further evidence has been sought on the question. The outstanding fact is that, in the Clemmensen reduction of 1-keto-octahydropyridocoline, base B, which is regarded as *cis*-octahydropyridocoline, is formed, whereas in all the other syntheses of the system, such as by the Clemmensen reduction of the 2- and 3-keto-octahydropyridocolines, base A, identical with norlupinane and regarded as the *trans*-form of (I), is alone produced.

In the first place it was decided to attempt to put the *cis–trans* hypothesis to the test of a crucial experiment. As *cis*- and *trans*-decahydroquinolines have been well characterised (Hückel and Stepf, *Annalen*, 1927, **453**, 170), *4-ketodecahydroquinoline* (II) has been prepared in order to test whether, in conformity with the foregoing, it would give *cis*- and *trans*-decahydroquinoline (III and IV) by the Clemmensen and the Wolff method respectively.

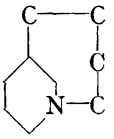


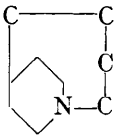
(I.) (II.) (III.) (IV.)

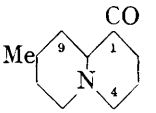
The compound (II) has been prepared by condensing ethyl hexahydroanthranilate and ethyl β-chloropropionate to give *ethyl* β-o-*carbethoxyhexahydroanilinopropionate*, which readily underwent ring closure by the Dieckmann method, and subsequent hydrolysis and decarboxylation gave (II). As only the *trans*-form of α-decalone can be obtained by ring closure methods, it is probable that the (II) thus produced is the *trans*-form. Hexahydroanthranilic acid, hitherto only prepared by the troublesome reduction of anthranilic acid with sodium and amyl alcohol (Einhorn and Meyenberg, *Ber.*, 1894, **27**, 2466), can be conveniently made by treating ethyl *cyclo*hexanone-2-carboxylate with dry ammonia and reducing the resulting ethyl tetrahydroanthranilate by means of hydrogen and platinum oxide. Reduction of (II) by both the Clemmensen and the Wolff method results in the formation of *trans*-decahydroquinoline. This is not surprising, since we have found that *cis*-decahydroquinoline is readily converted into the *trans*-isomer by boiling with hydrochloric acid. The Clemmensen reduction sometimes gives also a small amount of an isomeric base, apparently not *cis*-decahydroquinoline.

Failing a direct proof of the *cis-trans* nature of the bases B and A, further work has been done concurrently with the above on the alternative explanation that B is a structural isomer of (I), its objects being the synthesis of all the possible structural isomers and the

proof of the *cis-trans* hypothesis by the process of elimination. The preparation of 1-, 2-, and 3-methyloctahydropyrrocolines has been described (J., 1935, 1743; 1937, 1518). Other unlikely structural possibilities for B are (V) and (VI), and although these have not yet


(V.)


(VI.)


(VII.)

been prepared, the following evidence renders the structure (VI) extremely unlikely. 1-*Keto*-8-*methyloctahydropyridocoline* (VII) has been synthesised in the usual way from *ethyl* 4-*methylpiperidine*-2-*carboxylate*, in order to test whether the presence of the methyl group in position 8 had any effect on the course of the two reduction processes, as it was considered probable that it would inhibit the possibility of the conversion of ring system (VII) into (VI) during the Clemmensen reduction of the former. The reduction products, however, are in the main two isomeric *bases* corresponding to B and A, together with, in each case, an indication of the other theoretically predictable stereoisomer (due to the 8-methyl group) but in an amount insufficient for characterisation.

In striking difference from the decahydroquinolines, the B form of this base is not converted into the A form by sodium ethoxide in alcohol at 180°, nor the A form into the B by prolonged boiling with hydrochloric acid, thus illustrating that the octahydropyridocoline system is of much greater steric stability than the decahydroquinolines.

Experimental.

Ethyl Hexahydroanthranilate.—Ethyl Δ^1-tetrahydroanthranilate (Dieckmann, *Annalen*, 1901, **317**, 100) (25 g.) in glacial acetic acid (50 c.c.) was shaken with platinum oxide (0·15 g.) in hydrogen at 100 lb./sq. in. for 24 hours. The yellow viscous oil which remained on removal of the acetic acid was basified (saturated potassium carbonate solution) and extracted with ether; distillation of the dried extract gave ethyl hexahydroanthranilate (15 g., b. p. 115—120°/15 mm.) and a high-boiling fraction (9·5 g., b. p. 195—200°/15 mm.). The latter, on standing over-night with alcoholic hydrogen chloride, followed by 2 hours' refluxing, was converted into the above ethyl ester.

Ethyl β-o-*Carbethoxyhexahydroanilinopropionate.*—Ethyl hexahydroanthranilate (5 g.), ethyl β-chloropropionate (5 g.), and fused sodium acetate (3·5 g.) were heated for 18 hours at 100°, water (5 c.c.) added to dissolve sodium acetate and chloride, and the oil taken up in ether and dried; on distillation unchanged reactants (4 g., b. p. 60—100°/1 mm.) and the desired *ester* (5·2 g.), b. p. 135—140°/1 mm. (Found: C, 59·6; H, 9·0. $C_{14}H_{25}O_4N$ requires C, 59·3; H, 8·6%), were obtained.

4-*Ketodecahydroquinoline.*—The above ester (5·2 g.) in xylene (6 c.c.) was added to ice-cold powdered potassium (1·6 g.) suspended in xylene (8 c.c.), a yellow solid being deposited. After 1 hour's heating on the water-bath, the excess of potassium was destroyed with a few drops of alcohol, and concentrated hydrochloric acid (20 c.c.) added. The mixture was heated for 4 hours on the water-bath (evolution of carbon dioxide then ceased) and evaporated to dryness. The yellow residue was basified (saturated potassium carbonate solution) and extracted with ether, and the extract distilled, giving 4-*ketodecahydroquinoline* (1·4 g.), b. p. 135—140°/15 mm., as a stable colourless mobile oil (Found: C, 70·8; H, 10·1. $C_9H_{15}ON$ requires C, 70·6; H, 9·8%). The *picrate* crystallised from alcohol in light yellow needles, m. p. 175° (Found: C, 47·2; H, 4·6. $C_9H_{15}ON,C_6H_3O_7N_3$ requires C, 47·1; H, 4·7%), and the *picrolonate* in small, pale yellow plates, m. p. 201° (decomp.) (Found: C, 54·9; H, 5·2. $C_9H_{15}ON,C_{10}H_8O_5N_4$ requires C, 54·7; H, 5·5%).

4-*Keto*-1-*benzoyldecahydroquinoline.*—When the base (0·1 g.) and benzoyl chloride (0·1 g.) were kept in pyridine (2 c.c.) for 2 hours with frequent shaking, and water (5 c.c.) added, the *benzoyl* derivative was deposited. It crystallised from methyl alcohol in small prisms, m. p. 145° (Found: C, 74·9; H, 7·6. $C_{16}H_{19}O_2N$ requires C, 74·7; H, 7·5%).

Decahydroquinoline obtained by the Wolff Reduction.—4-Ketodecahydroquinoline (0·5 g.) was refluxed for 18 hours with hydrazine hydrate (2 c.c.). On cooling, the hydrazone (0·5 g.) was deposited. It was dissolved in alcohol (5 c.c.) and heated with sodium ethoxide (from

sodium, 0·4 g.) for 18 hours at 180°. The resulting mixture was dissolved in water, acidified (concentrated hydrochloric acid), and evaporated, the white residue basified (50% potassium hydroxide solution), and the base extracted with ether and distilled (0·15 g., b. p. 70—80°/15 mm.). It solidified in long white needles, m. p. 44°, identical with *trans*-decahydroquinoline (Found : C, 77·1; H, 11·9. Calc. for $C_9H_{17}N$: C, 77·7; H, 12·2%). The picrate crystallised from dry ether in small, pale yellow prisms, m. p. 157° (Found : C, 49·2; H, 5·0. Calc. for $C_9H_{17}N,C_6H_3O_7N_3$: C, 48·9; H, 5·4%). The *picrolonate* crystallised from alcohol in small wart-shaped clusters of yellow prisms, m. p. 202° (decomp.) (Found : C, 56·4; H, 6·0. $C_9H_{17}N,C_{10}H_8O_5N_4$ requires C, 56·6; H, 6·2%). The hydrochloride formed colourless prisms, m. p. 275°, from alcohol (Found : C, 61·4; H, 10·2. Calc. for $C_9H_{17}N,HCl$: C, 61·5; H, 10·25%). A higher-boiling fraction was also obtained (0·2 g., b. p. 130—140°/15 mm.), which solidified on standing and crystallised from light petroleum (b. p. 80—100°) in white prisms, m. p. 125° (Found : C, 68·0; H, 10·1%).

Decahydroquinoline obtained by the Clemmensen Reduction.—The 4-keto-compound (1 g.) was refluxed for 24 hours with concentrated hydrochloric acid (8 c.c.) and amalgamated zinc (5 g.). A further 5 g. of zinc and concentrated hydrochloric acid (10 c.c.) were added, and the mixture refluxed for a further 24 hours. The liquid was decanted from the excess of metal and evaporated to dryness, and the residue basified (50% potassium hydroxide solution) and steam-distilled (200 c.c.). The distillate was acidified and evaporated, the residue basified (50% potassium hydroxide solution), and the decahydroquinoline extracted and distilled (0·3 g., b. p. 70—80°/15 mm.). It was converted, by passing dry hydrogen chloride into an ethereal solution, into its hydrochloride, which crystallised from alcohol in colourless needles, m. p. 275° (Found : C, 61·4; H, 10·2. Calc. for $C_9H_{17}N,HCl$: C, 61·5; H, 10·25%). This was dissolved in a little water, the basified (50% potassium hydroxide solution) liquid shaken with ether, and the extract dried and mixed with an equivalent of picric acid in dry ether; *trans*-decahydroquinoline picrate was then obtained, m. p. alone or mixed with the product from the Wolff reduction, 157° (Found : C, 48·7; H, 5·3. Calc. for $C_9H_{17}N,C_6H_3O_7N_3$: C, 48·9; H, 5·4%). Concentration of the mother-liquor from the *trans*-decahydroquinoline hydrochloride and precipitation with ether gave a small quantity of a hydrochloride, m. p. 222°, which crystallised from alcohol–ether in prisms, m. p. 228°. This was converted into *picrate* as above, and gave orange-yellow prisms, m. p. 169°, depressed to 148° by admixture with the picrate of 4-ketodecahydroquinoline (Found : C, 49·2; H, 5·5. $C_9H_{17}N,C_6H_3O_7N_3$ requires C, 48·9; H, 5·4%).

cis- *and* trans-*Decahydroquinolines.*—Quinoline (10 g.) or tetrahydroquinoline (10 g.) was shaken with platinum oxide (0·2 g.) in acetic acid (20 c.c.) with hydrogen at 100 lb./sq. in. for 18 hours, platinum oxide (0·05 g.) added, and the whole again shaken with hydrogen for 2 hours. On working up, decahydroquinoline (9·5 g., b. p. 80—90°/15 mm.) was obtained. Fractional crystallisation of the hydrochlorides from alcohol, followed by conversion into picrates and crystallisation of these from alcohol–ether, gave the picrate of *cis*-decahydroquinoline, m. p. 144—145°, and that of the *trans*-compound, m. p. 157°. The bases recovered from these were identical with those described by Hückel and Stepf (*loc. cit.*).

Conversion of cis- *into* trans-*Decahydroquinoline.*—*cis*-Decahydroquinoline (0·5 g.) in concentrated hydrochloric acid (5 c.c.) was refluxed for 18 hours, the solution evaporated to dryness, and the residue crystallised from alcohol, giving the hydrochloride of the *trans*-base (0·45 g., m. p. 275° alone or mixed with an authentic specimen). Concentrated hydrochloric acid is without effect on the *trans*-hydrochloride, and neither the *cis*- nor the *trans*-base is affected by heating for 18 hours with sodium ethoxide in alcohol.

Ethyl 4-Methylpiperidine-2-carboxylate.—Crude 4-methylpiperidine-2-carboxylic acid (4 g.) (Clemo and Gourlay, this vol., p. 478) was dissolved in boiling amyl alcohol (200 c.c.), and sodium (16 g.) quickly added. When the metal had dissolved (about 1 hour), the solution was poured into water (200 c.c.), and the amyl alcohol extracted twice with dilute hydrochloric acid (200 c.c.). The aqueous liquid was taken to dryness, the residue extracted three times with boiling alcohol (75, 50, 50 c.c.), and the united extracts evaporated; the residue was dissolved in alcohol (25 c.c.), saturated with hydrogen chloride at 0°, and left for 18 hours. After refluxing for 2 hours, the alcohol was removed, and the residue basified (saturated potassium carbonate solution) and extracted with ether. Fractionation gave *ethyl 4-methylpiperidine-2-carboxylate* as a mobile oil (1·25 g.), b. p. 70°/1 mm. (Found : C, 63·3; H, 9·55. $C_9H_{17}O_2N$ requires C, 63·2; H, 9·9%). The *picrate* crystallised from ether in deep yellow prisms, m. p. 142° (Found : C, 45·1; H, 4·9. $C_9H_{17}O_2N,C_6H_3O_7N_3$ requires C, 45·0; H, 5·0%).

γ-2-Carbethoxy-4-methylpiperidinobutyronitrile.—The above ester (1·5 g.) was heated for 1 hour on the water-bath with γ-bromobutyronitrile (1·5 g.) and anhydrous potassium carbonate

(2 g.), water added to dissolve the potassium carbonate and bromide, and the oil extracted with ether. Distillation gave unchanged reactants (0·5 g., b. p. 60—80°/1 mm.) and *γ-2-carbethoxy-4-methylpiperidinobutyronitrile* (2 g.), b. p. 135°/1 mm., as a colourless mobile oil (Found: C, 65·8; H, 9·0. $C_{13}H_{22}O_2N_2$ requires C, 65·5; H, 9·2%).

Ethyl γ-2-Carbethoxy-4-methylpiperidinobutyrate.—The above nitrile (3 g.) was dissolved in alcohol (20 c.c.), and the solution saturated with hydrogen chloride, left overnight, and refluxed for 2 hours. The alcohol was removed, the residue basified and extracted, and the extract distilled, giving the *di-ester* as a colourless oil (2·5 g.), b. p. 136—138°/1 mm. (Found: C, 62·9; H, 9·5. $C_{15}H_{27}O_4N$ requires C, 63·1; H, 9·5%).

1-*Keto*-8-*methyloctahydropyridocoline.*—The di-ester (3 g.) in xylene (5 c.c.) was added to powdered potassium (1 g.) suspended in xylene (10 c.c.), and heated for 1 hour on the water-bath. Alcohol (1 c.c.), followed by concentrated hydrochloric acid (20 c.c.), was then added, the solution heated for 3 hours on the water-bath, the solvents removed under reduced pressure, and the residue basified (saturated potassium carbonate solution) and extracted with ether. Distillation gave the *ketone* as a pale yellow, unstable liquid (1·05 g.), b. p. 115—120°/15 mm. (Found: C, 71·2; H, 10·6. $C_{10}H_{17}ON$ requires C, 71·7; H, 10·2%). The *picrate* crystallised from alcohol in orange-yellow needles, m. p. 178° (decomp.) (Found: C, 48·5; H, 5·5. $C_{10}H_{17}ON,C_6H_3O_7N_3$ requires C, 48·5; H, 5·1%).

8-*Methyloctahydropyridocoline A obtained by the Wolff Reduction.*—The ketone (0·5 g.) was refluxed for 18 hours with hydrazine hydrate (3 c.c.), and the hydrazone extracted with ether and heated for 18 hours at 170° with sodium ethoxide (from sodium, 0·4 g.) in alcohol (2 c.c.). Water was added, the solution acidified (concentrated hydrochloric acid) and taken to dryness, and the residue basified (saturated potassium carbonate solution) and extracted with ether. Distillation gave 8-*methyloctahydropyridocoline A* as a colourless oil (0·34 g.), b. p. 47—48°/1 mm. (Found: C, 78·0; H, 12·6. $C_{10}H_{19}N$ requires C, 78·4; H, 12·4%). The *picrate* crystallised from alcohol in canary-yellow prisms, m. p. 150° (Found: C, 50·4; H, 5·6. $C_{10}N_{19}N,C_6H_3O_7N_3$ requires C, 50·3; H, 5·8%), and the *picrolonate* in small yellow prisms, m. p. 197° (Found: C, 57·7; H, 6·6. $C_{10}H_{19}N,C_{10}H_8O_5N_4$ requires C, 57·6; H, 6·5%). On concentration of the mother-liquor a very small quantity of a second form separated. The *methiodide* crystallised from acetone in colourless prisms, m. p. 212° (Found: C, 44·9; H, 7·7. $C_{10}H_{19}N,CH_3I$ requires C, 44·7; H, 7·0%).

8-*Methyloctahydropyridocoline B obtained by the Clemmensen Reduction.*—The ketone (0·5 g.), amalgamated zinc (5 g.), and concentrated hydrochloric acid (10 c.c.) were refluxed for 18 hours, and the solution decanted and taken to dryness. The residue was basified (50% potassium hydroxide solution) and steam-distilled, and the distillate acidified and evaporated. From the residue the *base* was liberated (saturated potassium carbonate solution), extracted with ether, and distilled (0·28 g., b. p. 47—48°/1 mm.) (Found: C, 78·1; H, 12·2%). The *picrate* crystallised from alcohol in deep yellow prisms, m. p. 189° (Found: C, 49·8; H, 5·4%) (on concentration of the mother-liquor a small quantity of a second picrate, m. p. 152°, was deposited), and the *picrolonate* in deep yellow clusters of small prisms, m. p. 138° (Found: C, 57·6; H, 6·7%). The *methiodide* crystallised from acetone in colourless prisms, m. p. 181° (Found: C, 44·9; H, 7·3%).

Attempted Interconversion of the A and the B Forms.—The B base (0·1 g.) was heated with sodium ethoxide (2 g.) and alcohol (2 c.c.) at 180° for 18 hours, and recovered unchanged (0·07 g.) as proved by conversion into picrate (m. p. alone or mixed, 189°). The A base (0·1 g.) was recovered unchanged (0·08 g.) after 18 hours' boiling with concentrated hydrochloric acid (picrate, m. p. alone or mixed, 150°).

Our thanks are due to Mr. W. A. Campbell for the micro-analyses, and one of us (J. G. C.) thanks the Council of King's College for a Post-Graduate Studentship.

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[*Received, June 9th*, 1938.]