277. *Synthetical and Stereochemical Investigations of Reduced Cyclic Bases. Part II. The* cis- *and* trans-*Decahydroquinolines.*

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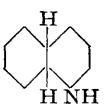
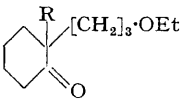
The two geometrically isomeric 2-(3′-*ethoxypropyl*)cyclo*hexylamines* have been prepared from 2-(3′-ethoxypropyl)*cyclo*hexanone. Ring-closure of the 3′-bromo-amines obtained by refluxing the isomerides with hydrobromic acid gave pure *cis*- and *trans*-decahydroquinolines which were identified by crystalline derivatives.

The octahydro-derivative formed in the direct hydrogenation of indole is, for reasons given in Part I (*J.*, 1945, 277), to be regarded as the *cis*-compound. None of the corresponding *trans*-base appears to be produced during the reduction, and in view of the comparatively strained condition of the *trans*-structure, it is unlikely that this, as yet unknown *trans*-octahydroindole will become available, except by some process involving ring-closure of a suitable monocyclic intermediate. It was therefore desirable to devise a synthesis applicable to those dicyclic amines not accessible by reduction methods, and as the relative merits of possible alternative routes are likely to be more readily determined where both forms of a given base are already known, the investigation was initially directed towards the synthesis of the decahydroquinolines (I).

The existence of both *cis*- and *trans*-decahydroquinolines was first clearly established by Hückel and Stepf (*Annalen*, 1927, **453**, 163) who showed that both forms are simultaneously produced during the catalytic hydrogenation of quinoline, the relative amounts of each depending on the experimental conditions. The amines were characterised by crystalline derivatives, and their stereochemical configurations allocated by application of the Auwers–Skita rule. *trans*-Decahydroquinoline has been derived from the synthetic 4-ketodecahydroquinoline by the Wolff and the Clemmensen method of reduction (Clemo, Cook, and Raper, *J.*, 1938, 1183), and it has recently been shown that this isomer is also formed in the sodium and alcohol reduction of 5 : 6 : 7 : 8-tetrahydroquinoline (Prelog and Szpilfogel, *Helv. Chim. Acta*, 1945, **28**, 1684). Methods of this kind, which depend on the hydrogenation of preformed dicyclic structures, are not suitable, however, for the preparation of both *cis*- and *trans*-forms when—as is the case with the two octahydroindoles—the isomerides differ appreciably in strain, since mere variation of the reduction conditions cannot apparently overcome the tendency to form the strainless *cis*-modification. Accordingly, the plan adopted in the following work was to prepare the two geometrical isomers of the 3′-bromopropyl*cyclo*hexylamine (III, R = Br) in the belief that on cyclisation they would afford the corresponding forms of decahydroquinoline.



(I.)



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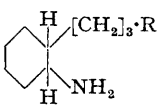

(III.)

The synthesis is analogous to that described in Part I (*loc. cit.*) for the preparation of the isomeric 2-ethyl*cyclo*hexylamines, and employs ethyl *cyclo*hexanone-2-carboxylate, of which the sodio-derivative was condensed with 3-ethoxypropyl bromide. Acid hydrolysis of the resulting *ethyl* 2-(3′-*ethoxypropyl*)cyclo*hexanone-2-carboxylate* (II; R = CO_2Et) also effected partial replacement of the ethoxy-group, but with refluxing barium hydroxide this complication was avoided and the desired ketone (II; R = H) was obtained in 42% yield, together with 32% of 2-(3′-*ethoxypropyl*)*pimelic acid*. By the action on the latter of acetic anhydride and distillation, a further quantity of the *cyclo*hexanone (II; R = H) was obtained, a 2 : 4-*dinitrophenylhydrazone* and *semicarbazone* identifying both specimens.

The *oxime* of the ketone (II; R = H) was reduced by sodium in boiling ethanol, giving in good yield an oily amine characterised by an evidently homogeneous *benzoyl* derivative. From its production under alkaline conditions the base was believed to be the *trans*-2-(3′-ethoxypropyl)-*cyclo*hexylamine (III; R = OEt), a conclusion which was later substantiated by its conversion into *trans*-decahydroquinoline. This was done by refluxing the pure recrystallised benzoyl compound with concentrated hydrobromic acid, which, by replacing both the ethoxy- and the benzoyl group, appeared to give, as hydrobromide, the *trans*-bromo-amine (III; R = Br). To effect ring-closure to *trans*-decahydroquinoline it was sufficient merely to keep the product with excess of ammonia, but the *N*-benzoyl group exhibited an unusual reluctance to hydrolyse, so the

amine was accompanied by a neutral compound, which is regarded as trans-2-(3′-*bromopropyl*)-cyclo*hexylbenzamide*.

Reduction of the ketoxime over Raney nickel in alcoholic ammonia led, on the other hand, to a mixture of the *cis*- and *trans*-isomers of (III; R = OEt). The greater insolubility of the *trans*-benzamide enabled a specimen of this compound to be separated in a pure condition, but on submitting the remainder of the reduction product to the action of boiling hydrobromic acid, basifying with ammonia, and shortly after extracting with ether, derivatives of both *cis*- and *trans*-decahydroquinoline were isolated. One of these, *trans*-decahydroquinoline hydrobromide, gradually crystallised from the ethereal extract, an indication of the relatively slow rate of cyclisation of the *trans*-bromo-amine.

From the ether-soluble residue, *trans*-decahydroquinoline hydrochloride was prepared, but the presence of the stereoisomeric amine was evident both on benzoylation and on treatment with aqueous picric acid, when the *cis*-benzoyl compound and the *cis*-picrate were isolated.

cis-Decahydroquinoline was more conveniently obtained from (II, R = H) by Leuckart's reaction, *viz.* heating under pressure with formamide. Part of the product (*ca.* 18%) solidified and could thus be separated; its conversion into *trans*-decahydroquinoline by hydrolysis with hydrobromic acid, etc., showed it to be trans-2-(3′-*ethoxypropyl*)cyclo*hexylformamide*. The bulk of the product, consisting of the *cis*-amide, when submitted to mild acid hydrolysis gave *cis*-2-(3′-ethoxypropyl)*cyclo*hexylamine, analysed as its *benzoyl*-derivative. Both the latter and the original *cis*-formamide were hydrolysed with boiling hydrobromic acid, and after being made alkaline, the product yielded *cis*-decahydroquinoline, as was shown by the properties of its hydrochloride and picrate. In agreement with the observations of Prelog and Szpilfogel (*loc. cit.*), no evidence was detected of the isomerisation of *cis*- to *trans*-decahydroquinoline hydrochloride on heating the former with concentrated hydrochloric acid (cf. Clemo, Cook, and Raper, *loc. cit.*).

Experimental.

Ethyl 2-(3′-*Ethoxypropyl*)cyclo*hexanone*-2-*carboxylate* (II; R = CO_2Et).—The sodio-compound precipitated on adding ethyl *cyclo*hexanone-2-carboxylate (63·5 g.) to a solution of sodium (8·9 g.) in absolute ethanol (190 c.c.) was treated with 3-ethoxypropyl bromide (63·5 g.), and the mixture refluxed for 4 hours on a steam-bath. Evaporation of the solution and addition of water gave ethyl 2-(3′-*ethoxypropyl*)cyclo*hexanone*-2-*carboxylate* (63·2 g., 66%), which distilled as a colourless oil, b. p. 167—168°/11 mm. (Found: C, 65·6; H, 9·4. $C_{14}H_{24}O_4$ requires C, 65·6; H, 9·4%). The 2 : 4-*dinitrophenylhydrazone* of the ester separated from light petroleum as a deep yellow micro-crystalline powder, m. p. 76° (Found: C, 54·7; H, 6·3; N, 13·1. $C_{20}H_{28}O_7N_4$ requires C, 55·0; H, 6·4; N, 12·9%).

2-(3′-*Ethoxypropyl*)cyclo*hexanone* (II; R = H).—The keto-ester (97 g.) was heated under reflux with a solution of baryta (208 g.) in water (560 c.c.) for 6 hours. On cooling, the liquid was acidified with concentrated hydrochloric acid, and the liberated oil extracted with ether. After being washed with 10% aqueous sodium hydroxide, the ethereal extract was dried and distilled, giving 2-(3′-ethoxypropyl)*cyclo*hexanone (29·6 g., 42%) of b. p. 128—129°/12 mm. Its 2 : 4-*dinitrophenylhydrazone* separated from aqueous alcohol as an orange microcrystalline powder, m. p. 77° (Found: C, 56·0; H, 6·5; N, 15·2. $C_{17}H_{24}O_5N_4$ requires C, 56·0; H, 6·6; N, 15·4%). The *semicarbazone*, colourless needles from light petroleum, had m. p. 96° (Found: C, 60·0; H, 9·4; N, 17·3. $C_{12}H_{23}O_2N_3$ requires C, 59·8; H, 9·5; N, 17·4%).

Acidification of the alkaline washings gave an oil, which was extracted with ether and distilled. The fraction, b. p. 243—248°/8 mm., consisted of 2-(3′-*ethoxypropyl*)*pimelic acid* (30·3 g., 32%), a colourless liquid, which very slowly solidified but could not be recrystallised from the usual solvents (Found: C, 58·1; H, 8·4. $C_{12}H_{22}O_5$ requires C, 58·5; H, 8·9%). Portions (10 g.) were heated with acetic anhydride (35 g.) under a short fractionating still-head, and when the temperature of the distillate reached 137° (after 6 hours), a further addition of acetic anhydride (15 g.) was made and the heating continued for 3 hours. After removal of the remaining anhydride, the residue was maintained at 215° for several hours, whereupon 3′-ethoxypropyl*cyclo*hexanone (1·7 g., 23%), b. p. 125—130°/10 mm., was again isolated and identified by its 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 77°, and semicarbazone, m. p. and mixed m. p. 96°. From the material obtained by slow distillation of the pimelic acid at 280—300° in presence of baryta (1%) no appreciable fraction corresponding to the desired ketone could be obtained.

trans-2-(3′-*Ethoxypropyl*)cyclo*hexylamine*.—The 3′-ethoxypropyl*cyclo*hexanone (11 g.), hydroxylamine hydrochloride (9 g.), and hydrated sodium acetate (14 g.) were heated in 60% alcohol (75 c.c.) for 3 hours under reflux. The *oxime* (10·4 g., 87%) was obtained by evaporation and ether extraction as a liquid, b. p. 163—164°/12 mm., which crystallised from light petroleum in colourless, long, narrow plates, m. p. 47° (Found: C, 66·1; H, 10·5; N, 7·2. $C_{11}H_{21}O_2N$ requires C, 66·4; H, 10·5; N, 7·0%).

A solution of the oxime (7 g.) in hot absolute alcohol (100 c.c.) was treated with pieces of sodium (total 8·6 g.), and the liquid heated under reflux until the metal had dissolved. The alcohol was then removed under suction after acidification with a mixture of concentrated hydrochloric acid (50 c.c.) and water (75 c.c.). Addition of excess potassium hydroxide and ether extraction gave the oily amine (III; R = OEt) (5 g., 77%), b. p. 114°/8 mm. It was rapidly contaminated by a layer of carbonate and was therefore characterised as a *benzoyl* derivative, which when crystallised from aqueous alcohol formed

colourless needles, m. p. 119° (Found : C, 74·7; H, 9·3; N, 4·5. $C_{18}H_{27}O_2N$ requires C, 74·7; H, 9·4; N, 4·9%).

trans-*Decahydroquinoline.*—*trans*-2-(3′-Ethoxypropyl)*cyclo*hexylbenzamide (2 g.), m. p. 119°, was heated in refluxing hydrobromic acid (50 c.c. of 50%) for 8 hours, and the product remaining on evaporation under reduced pressure was treated with aqueous ammonia and ether and left overnight. This led to the appearance of a sparingly soluble crystalline solid, a further quantity of which was obtained by evaporation of the ethereal layer, after washing with dilute acid. Recrystallisation from light petroleum gave the supposed trans-2-(3′-*bromopropyl*)cyclo*hexylbenzamide* as clusters of minute colourless needles, m. p. 127° (Found : C, 59·6; H, 6·8; N, 4·6; Br, 25·0. $C_{16}H_{22}ONBr$ requires C, 59·3; H, 6·8; N, 4·3; Br, 24·7%).

The liberated acid-soluble product of the foregoing reaction, dried over potassium hydroxide, was dissolved in anhydrous ether and treated with hydrogen chloride, whereby *trans*-decahydroquinoline hydrochloride (0·5 g., 41%) was precipitated. Crystallised from ethanol–ethyl acetate, it formed colourless plates, m. p. 278° (decomp.) (Found : C, 61·4; H, 10·2; N, 7·5; Cl, 19·5. Calc. for $C_9H_{17}N,HCl$: C, 61·5; H, 10·3; N, 8·0; Cl, 20·2%). The purified salt yielded *trans*-decahydroquinoline, b. p. 78—80°/15 mm., as long colourless needles, m. p. 48°.

Catalytic Reduction of 2-(3′-*Ethoxypropyl*)cyclo*hexanone Oxime.*—The oxime (10·4 g.), dissolved in ethanol (75 c.c.) saturated with ammonia, was hydrogenated over Raney nickel at 37 atm./130°. The filtered solution was acidified and heated to remove alcohol, after which addition of alkali and ether extraction yielded a base (7 g.), b. p. 119°/13—14 mm. Benzoylation of a specimen and crystallisation of the product gave the benzoyl compound, m. p. and mixed m. p. 119°, of the *trans*-amine (III; R = OEt).

After the reduction product (6·1 g.) had been refluxed with hydrobromic acid (122 c.c., 50%) for 5 hours, and evaporated to dryness, the residue was treated with aqueous ammonia and the amine then extracted with ether. On standing, *trans*-decahydroquinoline hydrobromide (0·4 g.), m. p. 278°, slowly separated (Found : C, 49·1; H, 8·1; N, 6·2; Br, 36·1. Calc. for $C_9H_{17}N,HBr$: C, 49·1; H, 8·1; N, 6·3; Br, 36·4%). The filtered ethereal solution (containing 3 g. of amine) gave with hydrogen chloride the *trans*-hydrochloride, but the recrystallised products of the action of aqueous picric acid and of benzoyl chloride consisted of *cis*-decahydroquinoline picrate (see below) and of the *cis*-benzoyl compound, m. p. (after 3 crystallisations from light petroleum) 96° (Found : C, 78·6; H, 8·5. Calc. for $C_{16}H_{21}ON$: C, 79·0; H, 8·6%).

cis-2-(3′-*Ethoxypropyl*)cyclo*hexylamine.*—2-(3′-Ethoxypropyl)*cyclo*hexanone (4·3 g.) and ammonium formate (7·2 g.) were heated in a sealed tube at 200° for 10 hours. The product was shaken with water and ether, the ethereal extract giving on distillation the mixed formamides (3·9 g., 78%), b. p. 187—191°/7 mm. The distillate became semi-solid, and by addition of a little light petroleum and filtration, it was separated into a crystalline solid and an oil (3·2 g.). The latter was heated under reflux with a mixture of concentrated hydrochloric acid (9 c.c.) and alcohol (9 c.c.) for 1½ hours. After being washed with ether, the solution was made alkaline, and the base isolated by ether and distilled. The fraction (1 g.) of b. p. 117°/11 mm. was benzoylated, and the cis-2-(3′-*ethoxypropyl*)cyclo*hexylbenzamide* obtained as a microcrystalline powder from light petroleum, m. p. 54° (Found : C, 74·4; H, 9·3; N, 4·8%).

The solid portion of the above reaction product crystallised from aqueous alcohol or light petroleum as minute needles, m. p. 84°, consisting of the trans-*ethoxypropyl*cyclo*hexylformamide* (Found : C, 67·4; H, 10·6; N, 6·5. $C_{12}H_{23}O_2N$ requires C, 67·6; H, 10·8; N, 6·5%). Hydrolysis of the amide (0·5 g.) with dilute hydrochloric acid (5 c.c. of 7%) on a steam-bath for 2 hours, followed by washing with ether, extraction of the basified solution and distillation, gave the *trans*-amine (III; R = OEt), identified by its benzoyl derivative, m. p. and mixed m. p. 119°. Hydrolysis of the formamide with boiling hydrobromic acid and isolation of the product as already described gave *trans*-decahydroquinoline hydrochloride in 61% yield.

cis-*Decahydroquinoline.*—The oily *cis*-2-(3′-ethoxypropyl)*cyclo*hexylformamide (2·0 g.) was heated with hydrobromic acid (45 c.c. of 50%) under reflux for 7 hours, and the substance left on evaporation of the acid under reduced pressure was basified with ammonia. By extracting with ether and treating the dried extract with hydrogen chloride, *cis*-decahydroquinoline hydrochloride (0·5 g.) was obtained as needles, m. p. 218° (decomp.) (Found : C, 59·9; H, 10·1; N, 7·7; Cl, 19·6. Calc. for $C_9H_{17}N,HCl$: C, 61·5; H, 10·3; N, 8·0; Cl, 20·2%). The *cis*-decahydroquinoline was also prepared from the *cis*-2-(3′-ethoxypropyl)*cyclo*hexylbenzamide, m. p. 54°, by hydrolysis with hydrobromic acid under similar conditions. The product was purified as hydrochloride, from which the base was recovered and converted into the picrate, yellow prisms from chloroform–light petroleum, m. p. 134° (Found : C, 48·4; H, 5·4; N, 15·4. Calc. for $C_9H_{17}N,C_6H_3O_7N_3$: C, 48·8; H, 5·4; N, 15·2%).

The *cis*-hydrochloride (0·2 g.), heated under reflux with concentrated hydrochloric acid for 21 hours, was recovered unchanged, having m. p. 217° when crystallised from ethanol–ethyl acetate. Owing to the comparative insolubility of the *trans*-salt, had any been formed under these conditions, it is improbable that it could have been overlooked. A similar experiment conducted in a sealed tube at 160° for 52 hours again confirmed the stability of the hydrochloride.

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