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Preparation of *cis*- and *trans*-Decahydroisoquinolines and of Bz-Tetrahydroisoquinoline

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Of the possible hydrogenated derivatives of isoquinoline, the *cis*- and *trans*-decahydro compounds, py-tetrahydroisoquinoline, and very recently bz-tetrahydroisoquinoline, have been prepared mainly by ring-synthetic methods.[2,3] The latter has lately gained importance as an intermediate in the synthesis of morphane.[4]

In this communication a simple method for the preparation of 5,6,7,8-tetrahydroisoquinoline (bz-tetrahydroisoquinoline), and of the pure *cis*- and *trans*-decahydroisoquinolines directly from quinoline is reported.

Skita obtained by catalytic hydrogenation of isoquinoline in glacial acetic acid with colloidal platinum a substance which was very probably largely *cis*-decahydroisoquinoline; the physical properties of his substance, however, suggest the presence of a certain amount of the *trans*-isomer.[5] We have found that the hydrogenation of isoquinoline in glacial acetic acid with a trace of sulfuric acid gives a mixture of decahydroisoquinoline which contains 70–80% of the *cis*-isomer and 20% of the *trans*-compound.[6] The *cis*-compound was readily isolated from the crude mixture of isomers as the pure picrate (m. p. 150°). On the other hand, if the mixture of isomers was subjected to dehydrogenation over palladium at 210°, a mixture of bases was formed, from which 10% of *trans*-decahydroisoquinoline, 10–25% of 5,6,7,8-tetrahydroisoquinoline and isoquinoline were isolated by fractional extraction with 0.1 *N* hydrochloric acid.[7] These relationships are summarized in the chart. The 5,6,7,8-tetrahydroisoquinoline alternately was prepared by boiling *cis*-decahydroisoquinoline in tetralin with selenium for forty eight hours.

These experiments demonstrate the striking fact that *cis*-decahydroisoquinoline is much more readily dehydrogenated than the corresponding *trans*-isomer, a behavior which parallels that of the decahydroquinolines, and, to a lesser extent, that of the decalins (Ehrenstein[7]). Model considerations suggest that the determining factor may lie in the relatively easier approach of the *cis*-compound to the catalyst in a configuration favorable to the removal of hydrogen atoms in pairs.[8]

Experimental[9]

***cis*-Decahydroisoquinoline.**—The catalytic perhydrogenation of isoquinoline[7] was effected at room temperature and normal pressure as follows: isoquinoline (reagent, 1 g.) was dissolved in glacial acetic acid (10 cc.) and five drops of concentrated sulfuric acid was added.[10] In the presence of 1 g. of platinum oxide the tetrahydro stage was reached after about forty minutes, and the decahydro state after about four to eight hours. Omission of the concentrated sulfuric acid or use of less catalyst blocked the hydrogenation at the tetrahydro stage. The catalyst was removed by filtration, the diluted solution was made strongly alkaline and extracted with ether. After evaporation of the ether the base was neutralized with hydrochloric acid and evaporated to dryness. The crystallized hydrochloride (1.24 g., over 90%) showed an unsharp melting point, 165°. It was converted into the picrate. The dry picrate (2.5 g.) was treated five

(1) Fellow of the Mathew T. Mellon Foundation.

(2) Helfer, *Helv. Chim. Acta*, **9**, 814 (1926).

(3) Schlittler and Merian, *ibid.*, **30**, 1339 (1947).

(4) *Cf.* Grewe, *Naturwiss.*, **33**, 333 (1946).

(5) Skita, *Ber.*, **57**, 1977 (1924).

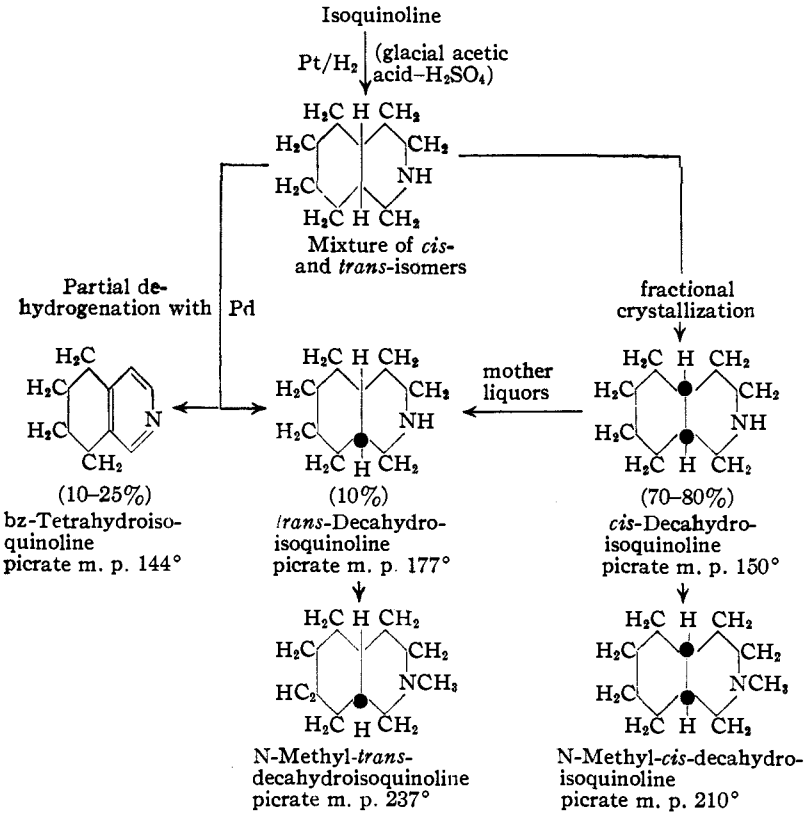
(6) In analogy with the catalytic hydrogenation of quinoline: both decahydroquinolines are formed in ratios dependent on the acidity of the solvent, Hückel and Stepf, *Ann.*, **453**, 163 (1934).

(7) All these reactions were observed in the quinoline series by Ehrenstein who developed the method of partial dehydrogenation and the procedure for the separation of the dehydrogenation products [*Ber.*, **67**, 1715 (1934)].

(8) *Cf.* Linstead, THIS JOURNAL, **64**, 1985 (1942), on the stereochemistry of catalytic hydrogenation.

(9) All melting points corrected.

(10) Kindler and Kwok, *Ann.*, **554**, 9 (1942).



times with 1–2 cc. of cold methanol, which chiefly removed *trans*-decahydroisoquinoline. The residue was dissolved in hot methanol and filtered after an hour from the crystals which separated. The final solution yielded uniform crystals which were recrystallized twice from methanol; melting point 150° (1.91 g., 73%). The picrate was converted into the hydrochloride by adding hydrochloric acid to the methanolic solution and extracting the picric acid with ether. The dry hydrochloride was treated with 1 cc. of absolute alcohol and the residue was crystallized from alcohol–ether. The beautifully crystallized hydrochloride melted sharply at 183° (0.41 g.).

N-Methyl-*cis*-decahydroisoquinoline Picrate.—The above hydrochloride (100 mg.) was boiled under reflux with 2 cc. of 95% formic acid and 2 cc. of 40% aqueous formaldehyde for two hours. The solution was evaporated to dryness and converted into the picrate. The picrate of the N-methyl base is much less soluble in methanol than that of the original base. It crystallizes from methanol in tufts of small needles, m. p. 210°, yield over 90%.

Anal. Calcd. for $C_{10}H_{19}N\cdot C_6H_3O_7N_3$: C, 50.26; H, 5.7. Found: C, 50.52; H, 5.45.

***trans*-Decahydroisoquinoline. A. By Fractional Crystallization.**—The combined cold methanol extracts of the *cis*-picrate contained mainly *trans*-compound. It could be obtained by careful slow fractional crystallization. The *trans*-picrate formed large prisms possessing a full yellow color and was separated mechanically from smaller light yellow aggregates of crystals that consisted chiefly of *cis*-picrate. The recrystallized *trans*-picrate melted at 175–178°.

B. By Dehydrogenation of the Accompanying *cis*-Compound.—The mixture of the *cis*- and *trans*-bases (1 g.), as obtained directly by hydrogenation, was heated under reflux with 0.2 g. of palladium black. The reaction was carried out in an apparatus similar to the one designed by H. Heymann.[11] After about four hours 650 cc. of hydrogen was evolved. The major part of the reaction mixture was distilled at 210° (760 mm.). The distillate was taken up in 20 cc. of ether and extracted with consecutive portions of 2 cc. of 0.1 *N* hydrochloric acid. Every fraction was converted separately into the picrate. The fractions 1–4 (Table I) were recrystallized from absolute methanol. The accompanying small amount of isoquinoline picrate could be easily separated owing to its much smaller solubility. The pure *trans*-decahydroisoquinoline picrate melted at 177°. On admixture with the *cis*-picrate (m. p. 150°) the melting point was depressed to 143°.

Anal. Calcd. for $C_9H_{17}N\cdot C_6H_3O_7N_3$: C, 48.91; H, 5.44. Found: C, 49.07; H, 5.38.

Hydrochloride.—The picrate was dissolved in methanol, treated with hydrochloric acid and ether; the aqueous solution after evaporation left the hydrochloride which crystallized from alcohol in needles, m. p. 224°. The salt is not very hygroscopic.

Anal. Calcd. for $C_9H_{17}N\cdot HCl$: C, 61.5; H, 9.8. Found: C, 61.1; H, 10.2.

Dehydrogenation.—Treatment of 30 mg. of the above chloride with 30 mg. palladium at 210° for one-half hour failed to have any dehydrogenating effect (the *cis*-chloride was easily converted into isoquinoline under these conditions). When 30 mg. of *trans*-base was heated with 90 mg. of palladium for three hours under reflux, one obtained a reaction product which was no longer miscible with water, picrate 223°, identical with isoquinoline picrate.

TABLE I

The melting points (cor.) were carried out on a micro hot stage; the figures in parentheses are sintering points.

Picrate fraction no.	Weight, mg.	Appearance	M. p., °C.	Compound
1		lemon-yellow, crystalline	170 (160)	*Trans*-decahydro isoquinoline (isoquinoline)
2	260		167 (160)	
3			169	
4			168	
5	67	amorphous	130	intermediate fraction
6		glistening needles, pale-yellow	158 (rest 168)	Bz-tetrahydroisoquinoline (isoquinoline)
7	270		155 (rest 175)	
8			155 (rest 180)	
9			155 (rest 180)	
10	65	mixture	190 (158)	intermediate fraction
11	70	small crystals	200 (185)	isoquinoline
12	67	dull, bright yellow	215 (190)	
13	68		220	
14	65		221	
15 etc.	65		223	

N-Methyl-*trans*-decahydroisoquinoline Picrate.—The compound was prepared in exactly the same way as described for the corresponding *cis*-compound. The picrate crystallized from methanol in thin needles which underwent crystalline transformation at 215° and melted at 237°.

(11) L. F. Fieser, "Experiments in Organic Chem.," 1941, p. 462.

Anal. Calcd. for $C_{10}H_{19}N \cdot C_6H_3O_7N_3$: C, 50.26; H, 5.7. Found: C, 50.57; H, 5.75.

Bz-Tetrahydroisoquinoline. A. By Partial Dehydrogenation with Palladium Black.—The picrate fractions 6–9 (Table I) were combined (270 mg.) and freed from the much less soluble isoquinoline picrate by sufficient recrystallizations from acetone. The pure product finally crystallized in golden-yellow needles of uniform appearance, m. p. 144°.

Anal. Calcd. for $C_9H_{11}N \cdot C_6H_3O_7N_3$: C, 49.73; H, 3.87. Found: C, 50.25; H, 3.87.

In another experiment, starting with the same amount (1 g.) of decahydro bases, dehydrogenation was stopped after the evolution of 310 cc. of hydrogen (calcd. for 5 moles of hydrogen, 781 cc.). In this case the medium fractions yielded 690 mg. of picrate, corresponding to about 25% yield of Bz-tetrahydroisoquinoline.

Picrolonate.—The free base, prepared from the above picrate, had a smell reminiscent of substituted pyridines (*e. g.*, collidine). Aqueous picrolonic acid precipitated from the solution of the hydrochloride the picrolonate which, recrystallized from methanol, melted at 214°.

Anal. Calcd. for $C_{19}H_{19}O_5N_5$: C, 57.43; H, 4.78. Found: C, 57.94; H, 5.03.

B. By Partial Dehydrogenation with Selenium in Tetralin.—*cis*-Decahydroisoquinoline (0.8 g.) was boiled under reflux in 15 cc. of freshly distilled tetralin with 0.5 g. of black selenium dust for forty-eight hours. The reaction mixture was filtered from the selenium, diluted with ether and extracted with 2-cc. portions of 0.1 *N* hydrochloric acid. The fractions were converted into the picrates, which had the properties: 1–3, *cis*-decahydroisoquinoline picrate (0.19 g.), m. p. 150°; 4, mixture, not crystallized, sticky; 5, Bz-tetrahydroisoquinoline picrate, m. p. (after removal of little accompanying isoquinoline picrate) 144°; 6, isoquinoline picrate, m. p. 223°. After evaporation of the ether and tetralin a small amount of naphthalene was obtained.

Summary

Catalytic hydrogenation of isoquinoline in glacial acetic acid with sulfuric acid leads to a mixture containing 70–80% *cis*- and at least 10% *trans*-isomer. The *cis*-isomer is more readily dehydrogenated with Pd than the *trans* isomer. By controlled dehydrogenation of the *cis*-isomer bz-tetrahydroisoquinoline was obtained.

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Some Basically Substituted Quinoxalines

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Of the many thousands of compounds synthesized and tested for antimalarial activity, those which have shown by far the greater promise, in general, are the derivatives of nitrogen-containing heterocycles bearing basic side chains, in particular the derivatives of quinoline. At the inception of this investigation very few basically substituted quinoxalines had been described in the chemical literature and even fewer had been tested for *antimalarial* activity.[1] Since quinoxaline differs from quinoline only in having a tertiary nitrogen substituted for the carbon in the 4-position of the ring, derivatives of quinoxaline appeared to have some interest as antimalarials.

In order to explore this possibility, a series of substituted aminoquinoxalines and their 2,5-dimethyl-1-pyrryl derivatives was prepared and subjected to pharmacological testing. In addition the rather high tuberculocidal activity of some related types of compounds prompted the synthesis of 2,3-bis-(*p*-aminophenyl)-quinoxaline, 2,3-bis-(*p*-hydroxyphenyl)-quinoxaline and 2,3-bis-(*p*-hydroxyphenyl)-6-aminoquinoxaline.

(1) While this investigation was in progress and since its completion three years ago, several papers have appeared dealing with the synthesis of quinoxaline derivatives for pharmacological purposes, *viz.*, (a) Gowenlock, Newbold and Spring, *J. Chem. Soc.*, 622 (1945); (b) Hall and Turner, *ibid.*, 699 (1945); (c) King and Beer, *ibid.*, 792 (1945); (d) Gawron and Spoerri, THIS JOURNAL, **67**, 514 (1945); (e) Mizzoni and Spoerri, *ibid.*, **67**, 1652 (1945); (f) Cavagnol and Wiselogle, *ibid.*, **69**, 795 (1947); (g) Stevens, Pfister and Wolf, *ibid.*, **68**, 1035 (1946); (h) Weijlard, Tishler and Erickson, *ibid.*, **66**, 1957 (1944); (i) Linsker and Evans, *ibid.*, **68**, 874 (1946); and (j) Wiedling, *Acta Path. Microbiol. Scand.*, **22**, 379 (1945), as well as a few notes.

The quinoxaline nuclei of the compounds synthesized in the course of this work were prepared by condensing appropriately substituted α-diketones with either *o*-phenylenediamine or 1,2,4-triaminobenzene dihydrochloride in acetic acid or aqueous ethanol solutions, respectively. In all cases the yields were satisfactory, although in the latter case, the removal of resinous by-products was troublesome.

The 1,2,4-triaminobenzene required was prepared and used in the form of its dihydrochloride. The original method of Hinsberg[2] for its preparation did not prove to be satisfactory. The complex formed between the amine and chlorostannous(ic) acids was often difficult to decompose completely and a tin-containing product was secured only difficultly purified by recrystallization. In addition, the frequent exposure to the air entailed in this process was deleterious to the very easily oxidized polyamine. In order to circumvent these difficulties, it was found that the catalytic reduction of 2,4-dinitroaniline in ethanol over Raney nickel was more rapid, convenient, and less expensive than the former method, and it yielded the product desired in greater yields of at least equal purity.

In the preparation of substituted benzoins, the experimental conditions necessary in order to get good yields of crystalline products are often quite rigid.[3] Rather than isolate the intermediate benzoins, anisoin and *o,o'*-dichlorobenzoin, in the prep-

(2) Hinsberg, *Ber.*, **19**, 1253 (1886).

(3) Dewar and Read, *J. Soc. Chem. Ind.*, **55T**, 347T (1936).