378. *The Phenazine Series. Part IV. The Octa- and Per-hydrophenazines.*

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IN Part III (this vol., p. 258) we stated that the methods of preparation of two isomeric 1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydrophenazines indicated the compound of m. p. 147° to be the *cis*-, and that of m. p. 156° to be the *trans*-isomer; of these, the latter is dissymmetric and should be resolvable. Attempts to resolve both compounds with tartaric, malic, camphorsulphonic, and bromocamphorsulphonic acids have, however, been unsuccessful; but, failing this direct evidence, we offer confirmation of the above hypothetical structures by a comparison of the physical properties of the isomers.

Auwers (*Annalen*, 1920, **420**, 92), from his investigation of ethylenic and homocyclic geometrical isomers, stated that the *cis*-compound usually possessed the higher boiling point (liquid), density, and refractive index; Skita, investigating homocyclic compounds, made the generalisation that in the hydrogenation of an unsaturated compound acid and alkaline reduction lead to the production of the *cis*- and the *trans*-isomer respectively. A review of the data recorded for fused heterocyclic systems indicates that the Auwers–Skita rule extends to such compounds without exception. In addition, the melting point of the *cis*-compound is lower than that of the *trans*, though Werner (" Lehrbuch," p. 172) stated that melting point and solubility were not certain criteria of configuration in ethylenic and homocyclic geometrical isomers. Values obtained for the octahydrophenazines at present under investigation, given in the table below, definitely indicate the compound, m. p. 147°, to be the *cis*-isomer.

Isomer.	M. p.	$a^{20°}$.	$d^{182°}$.	$n_D^{20°}$ (calc.).	Sol. in alcohol, % (*w*/*v*), 20°.	Sol. in ether, % (*w*/*v*), 20°.
cis	147°	1·1949	1·0064	1·6182	18·1	19·1
trans	156	1·1989	0·9982	1·6146	23·6	17·8

Although the densities of the compounds determined in the liquid state (at 182° by a pyknometric method) are in agreement with the Auwers–Skita rule, in the solid state the *trans*-compound is the denser. The refractive index of each isomer was calculated from values obtained for solutions in pyridine of several concentrations, which obeyed the mixture law. The order of solubilities of the two isomers is different in different solvents (compare Werner, *op. cit.*).

Reduction of 1 : 2 : 3 : 4-tetrahydrophenazine with sodium, which normally leads to the *trans*-compound, produces mainly the *cis*- in the presence of acetic acid; in this, and in a tin–hydrochloric acid reduction, the *cis*-form is accompanied by a small amount of the *trans*-; this has also been observed during analogous reductions of tetrahydrocarbazole (J., 1924, **125**, 1503; 1927, 2676) and tetrahydroacridine (J., 1924, **125**, 2437). In the present case, the reaction mixture can be readily separated by means of the insoluble tartrate formed in alcoholic solution by the *trans*-compound.

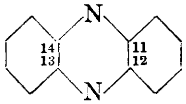
Further reduction of these three octahydrophenazines has led to the production of three perhydro(14H)-phenazines, which are essentially the same as the compounds described by Godchot and Mousseron (*Bull. Soc. chim.*, 1932, **51**, 528) as being produced by the reduction of 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydrophenazine. The terms α, β, and γ used by those authors are here used to designate the isomers, m. p. 135° (dinitroso-deriv., m. p.

168°; dipicrate, m. p. 278°), m. p. 95° (dinitroso-deriv., m. p. 183°; dipicrate, m. p. 252°), and m. p. 62° (dinitroso-deriv., m. p. 107°; dipicrate, m. p. 242°) respectively.

The various methods by which we have prepared these compounds, and the results of their attempted interconversions, are summarised in Table I.

1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-Octahydrophenazine is reduced in acetic acid solution by platinum–hydrogen under 100 lb./sq. in. to a mixture of all three isomeric perhydrophenazines. A consideration of the structures of the isomers possible in this type of compound shows that in only two of these are the hydrogen atoms of both junctions arranged in the *cis*-positions; in the production of this mixture of isomers, therefore, the platinum–acetic acid reagent has deviated from the simple Skita rule (see above) in at least one instance. It was not, however, found possible to cause the isomerisation of any of these compounds by a shaking in glacial acetic acid in the presence of platinum under the conditions of the reduction.

+ +	+ −	+ −	− −	− +
+ +	+ −	+ +	+ +	+ −
(I.)	(II.)	(III.)	(IV.)	(V.)



(The isomers are referred to in terms of the hydrogen atoms attached to carbon atoms 11, 12, 13, and 14 of the phenazine nucleus, which are represented by + if above and by − if below the mean plane of these C atoms.)

The observation that isomeride α is the product of a great number of reductions (reactions 1, 2, 4, 5, 7, and 10 in Table I) and the fact that it is the sole product of isomerisation in the perhydrophenazines (reactions 14, 16) indicates it to be a very stable compound. In all comparable cases of *cis-trans* isomerism investigated (Alder and Stein, *Annalen*, 1933, **501**, 247; Chuang and Tien, *Ber.*, 1936, **69**, 26; Zelinsky and Turowa-Pollak, *Ber.*, 1925, **58**, 1292, 1298; 1932, **65**, 1299), the *trans* is the stable product. It appears probable, therefore, that isomeride α possesses at least one *trans* junction; that it is not a normal product in the reduction 4 is indicated by the failure of Godchot and Mousseron (*loc. cit.*, p. 368) to detect it in the product of reduction of 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydrophenazine and of phenazine itself in glacial acetic acid by hydrogen at only a little over atmospheric pressure, and catalysed by platinum. Confirmation of this suggested structure is afforded by reactions 14 and 16 in view of the observation of Margolis (*Ber.*, 1936, **69**, 1710) that in substituted *cyclo*hexanes the equilibrium *cis* $\rightleftharpoons$ *trans* is moved in favour

TABLE I.

Initial Materials.	Reducing Agents.	Products.
1 : 2 : 3 : 4-Tetrahydrophenazine	1. H_2–Pt	*cis*-Octahydro- and α-perhydro-phenazine
	2. H_2–Ni-*A* at 140°	α-Perhydro- and *s*-octahydro-phenazine.
	3. H_2–Ni-*B* at 140°	*cis*-Octahydro- and *trans*-octahydrophenazine (little)
s-Octahydrophenazine	4. H_2–Pt	α-, β-, and γ-Perhydrophenazine
	5. H_2–Ni-*A* at 140°	α-Perhydrophenazine
	6. H_2–Ni-*B* at 140°	No change
cis-Octahydrophenazine	7. H_2–Pt; 8, H_2–Ni-*A* at 140°	α-Perhydrophenazine
	9. H_2–Ni-*B* at 140°	*trans*-Octahydrophenazine
trans-Octahydrophenazine ...	10. H_2–Pt; 11, H_2–Ni-*A* at 140°	α-Perhydrophenazine
	12. H_2–Ni-*B*	No change
α-Perhydrophenazine	13. H_2–Ni-*A* and -*B* at 140°; H_2SO_4; HCl; recovery from NO-cmpd.	No change
β-Perhydrophenazine	14. H_2–Ni-*A*, 140°	α-Perhydrophenazine
	15. Ni-*B*; H_2SO_4; HCl; recovery from NO-cmpd.	No change
γ-Perhydrophenazine	16. H_2–Ni-*A*, 140°	α-Perhydrophenazine
	17. Ni-*B*; H_2SO_4; HCl recovery from NO-cmpd.	No change

(For the definition of Ni-*A* and Ni-*B*, see this vol., p. 258.)

of the latter by a nickel catalyst. It is also noteworthy that isomerisation must have taken place in at least one instance during the production of isomeride α from *cis*- and *trans*-octahydrophenazine by reactions 7 and 10.

Attempted resolutions of the perhydrophenazines with camphorsulphonic, bromocamphorsulphonic, and tartaric acids have failed to yield an active compound. This negative evidence, which would confirm the *cis-cis* structures (I) and (II) for isomerides β and γ, and suggest structure (IV) for isomeride α, cannot, however, be relied upon, especially in view of the failure to resolve the octahydraphenazines.

Godchot and Mousseron (*loc. cit.*) succeeded in dehydrogenating the α- and β-perhydrophenazines by means of zinc dust, though this method affords only a poor yield. We have found that all three perhydrophenazines, in common with other reduced phenazine compounds (this vol., p. 258), are smoothly dehydrogenated by means of palladium–charcoal, giving yields of phenazine approaching the theoretical.

EXPERIMENTAL.

Acid–Metal Reductions of 1 : 2 : 3 : 4-*Tetrahydrophenazine*.—(1) The base (0·5 g.) was refluxed in alcohol (10 c.c.), and glacial acetic acid (15 c.c., 50% alcoholic) and sodium (2·5 g.) were added alternately in small amounts during ¾ hour so that the solution remained acid but the reaction did not proceed too vigorously. The product was poured into water, basified (sodium hydroxide solution), and extracted with ether, the solvent removed from the extract, and the residual bases dissolved in absolute alcohol (20 c.c.). The solution was boiled, *d*-tartaric acid (0·2 g.) added, and after ½ hour the precipitated trans-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydrophenazine* d-*tartrate* (0·02 g.), m. p. 222° (Found : C, 63·85; H, 6·9. $2C_{12}H_{16}N_2,C_4H_6O_6$ requires C, 63·9; H, 7·2%), was collected, and the base recovered by trituration with water (0·015 g., m. p. 156°). The residue left on removal of solvent from the alcoholic mother-liquor was basified (sodium hydroxide solution) and shaken with water and ether, and the *cis*-1 : 2 : 3 : 4 : 9 : 10 :11 : 12-octahydrophenazine obtained from the ethereal solution (0·3 g., m. p. 146°) crystallised from alcohol.

(2) The base (0·5 g.) was dissolved in warm concentrated hydrochloric acid (20 c.c.), and tin (4·0 g.—a large excess; less gave partly reduced products) added; the initially deep green solution became finally colourless, and the *cis* (0·4 g.) and the *trans* (0·05 g.)-octahydrophenazine were separated by the above method.

α-*Perhydrophenazine*.—(1) 1 : 2 : 3 : 4-Tetrahydrophenazine (5 g.) was passed in a stream of hydrogen over nickel catalyst *A* at 140° during 3 days and yielded a mixture which could not be separated by fractional crystallisation. To the product in hot alcohol (100 c.c.), excess of *d*-tartaric acid was added, and the precipitated α-perhydrophenazine *d*-tartrate collected (3·8 g., m. p. 315°) (Found : C, 48·4; H, 8·65. Calc. for $C_{12}H_{22}N_2,C_4H_6O_6,3H_2O$: C,48·2; H, 8·6%). The base was recovered by ether extraction of the basified solution of its salt, and separated from benzene in colourless needles, m. p. 135° (Found : C, 74·4; H, 11·5. Calc. for $C_{12}H_{22}N_2$: C, 74·2; H, 11·3%). Concentration of the alcoholic mother-liquor caused the separation of 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydrophenazine (1·4 g.), and a little unchanged tetrahydro-compound remained in solution. The amount of reduced products increases with increasing time of passage.

(2) Each of the three octahydrophenazines (1·0 g.), when reduced for 3 days in the manner described immediately above, yielded only α-perhydrophenazine (0·5 g.). The separation of the *d*-tartrates of α-perhydrophenazine and *trans*-octahydrophenazine, which were precipitated together when the product of reduction of the latter compound was worked up by the above method, was effected by trituration with water, which decomposed only the octahydrophenazine salt.

(3) Isomerides β and γ (0·5 g.) were passed separately over nickel catalyst *A* in the manner described above, the catalyst extracted with hot alcohol, and the α-perhydrophenazine crystallised (0·25 g.). The mother-liquor, when separated by the urate method, was found to contain only the α-isomeride and initial material.

(4) 1 : 2 : 3 : 4-Tetrahydrophenazine (1 g.), platinum oxide (0·05 g.), and glacial acetic acid (10 c.c.) were shaken in hydrogen (100 lb./sq. in.) for 20 hours. The yellow solution became colourless; the catalyst was removed by filtration, the filtrate basified (sodium hydroxide) and extracted with ether, the residue after removal of solvent dissolved in hot alcohol (20 c.c.), and *d*-tartaric acid (0·5 g.) added. The precipitated α-perhydrophenazine *d*-tartrate was

collected, and the base recovered as described above (0·2 g.). The alcoholic mother-liquor on concentration yielded *cis*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydrophenazine (0·7 g.).

By the above method, both of the 1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydrophenazines yielded only α-perhydrophenazine.

β- and γ-Perhydrophenazines.—1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-Octahydrophenazine (5·0 g.), platinum oxide (0·3 g.), and glacial acetic acid (15 c.c.) were shaken in hydrogen (100 lb./sq. in.) for 20 hours. Water was added to dissolve the salt produced, and the solution basified (sodium hydroxide) and extracted with ether. The mixture of bases (5 g.) left on removal of solvent could not be completely separated by fractional crystallisation, and only partly by crystallisation of the tartrates of nitroso-compounds (compare Godchot and Mousseron, *loc. cit.*, who separated the β- and the γ-isomeride by means of their nitroso-derivatives, and indicated a difference to exist in the solubilities of the urates of the bases).

The mixture was well shaken in hot water (120 c.c.) with uric acid (5·0 g.), and the insoluble portion was removed, basified, and extracted with light petroleum, from which β-perhydrophenazine (1·8 g., m. p. 95°) (Found : C, 74·4; H, 11·7. Calc. for $C_{12}H_{22}N_2$: C, 74·2; H, 11·3%) crystallised, on concentration, in stout colourless prisms. The base absorbs carbon dioxide from the air to yield a compound, m. p. 105—110°; the m. p. of 107° recorded by Godchot and Mousseron (*loc. cit.*) for a base (dinitroso-derivative, m. p. 182—183°) prepared in a similar manner is attributed to this phenomenon, for a repetition of their process led to β-perhydrophenazine, m. p. 95° (dinitroso-derivative, m. p. 183°).

The bases recovered from the more soluble urates were fractionally crystallised from light petroleum, yielding α-perhydrophenazine (0·4 g.) and the γ-isomeride (1·5 g.). A further quantity of each isomeride could be separated from the combined mother-liquors by repeating the urate separation. The occurrence of α-perhydrophenazine urate in this fraction can be reconciled with its lesser solubility reported by Godchot and Mousseron by the small amount present. Reduction over a longer period or with a greater amount of catalyst produced the same result.

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