

COMMUNICATIONS TO THE EDITOR

The Configuration of "Isocarvomenthylamine" and the Carvyl- and Carvotanacetylaminines

Sir:

"(-)-Isocarvomenthylamine" obtained^{1,2} from the (-)-isocarvomenthone oximes (I) by reduction with sodium and ethanol has been assigned³ the configuration (and conformation) II, since such reduction usually gives the equatorial product^{4,5} and since the oximes (*syn* or *anti*) were believed to exist nearly exclusively in conformation Ib. Configuration II seemed to be supported by the fact that the amine with nitrous acid gave, in good yield, the alcohol "(-)-isocarvomenthol"^{1b,2b} assumed³ to have configuration III, since it is known^{5,6} that equatorial amines with nitrous acid give alcohols of retained configuration. Recently, however, it has become clear⁷ that, contrary to the assumption of Bose³ but in agreement with the earlier, tentative assignments^{1,8} (-)-isocarvomenthol has, in fact, the configuration IV. Since recent work has indicated⁹ that isopropyl is only slightly larger than methyl, IV will exist predominantly in conformation IVa (in which the hydroxyl group is equatorial) rather than IVb. This, of course, throws grave doubt on the configurational assignment of "(-)-isocarvomenthylamine" as II, since it is not clear how nitrous acid deamination of II could give IV, unless II existed in the very unlikely alternative conformation (isopropyl and amino *syn*-axial) which might be deaminated with inversion of configuration.

We now wish to present conclusive evidence that "(-)-isocarvomenthylamine," in fact, has configuration V.

The known^{1,2} benzoyl derivative of "(-)-isocarvomenthylamine," m.p. 153°, [α]_D -40.0°, was obtained¹⁰ from the known¹¹ benzoyl derivative of (+)-*trans*-carvylamine (VI), m.p. 114°, [α]_D +250°, by catalytic reduction over Raney nickel. Amine VI was obtained, along with (-)-*cis*-carvylamine (VII), benzoyl derivative¹¹ m.p. 169°, [α]_D -96°, by zinc dust reduction of (+)-carvone oxime (VIII),¹² m.p. 72.5-73.5°, [α]_D +45.2°; the two amines (ratio of VI:VII about 2 by

(1) (a) R. G. Johnston and J. Read, *J. Chem. Soc.*, 226 (1934); (b) *ibid.*, 1138 (1935).

(2) (a) W. Hüchel and W. Doll, *Ann.*, **526**, 103 (1936); (b) W. Hüchel, *ibid.*, **533**, 1 (1938).

(3) A. K. Bose, *Experientia*, **8**, 458 (1952).

(4) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).

(5) J. A. Mills, *ibid.*, 260 (1953).

(6) A. K. Bose, *Experientia*, **9**, 256 (1953).

(7) E.g., A. Blumann, E. W. Della, C. A. Henrick, J. Hodgkin, and P. R. Jefferies, *Australian J. Chem.*, **15**, 290 (1962); Z. Chabudzinski, Z. Rykowski, and H. Kuczynski, *Roczniki Chem.*, **37**, 1571 (1963); G. O. Schenck, K. Gollnick, G. Buchwald, G. Ohloff, and S. Schroeter, *Ann.*, in press; E. E. Royals and J. C. Leffingwell, *J. Am. Chem. Soc.*, **86**, 2067 (1964).

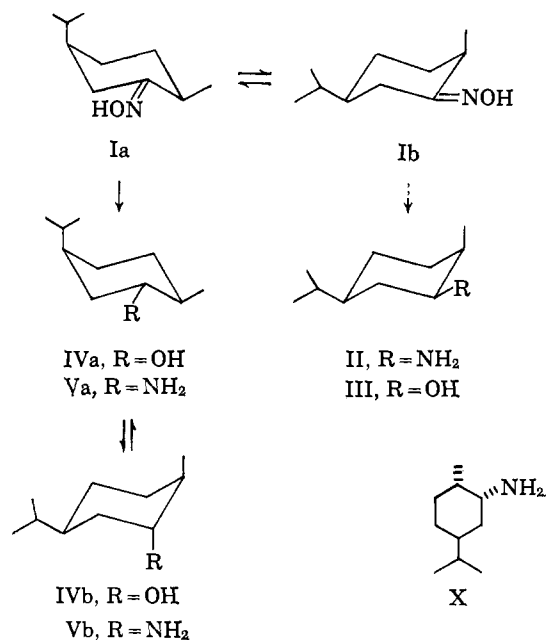
(8) See also H. D. Orloff, *Chem. Rev.*, **54**, 375 (1954).

(9) N. L. Allinger and S.-E. Hu, *J. Org. Chem.*, **27**, 3417 (1962); A. H. Lewin and S. Winstein, *J. Am. Chem. Soc.*, **84**, 2464 (1962); E. L. Eliel and T. J. Brett, Abstracts, 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963, p. 19Q; N. Mori and F. Suda, *Bull. Chem. Soc. Japan*, **36**, 227 (1963).

(10) All rotations were measured in chloroform at 20-25°. Actually the observed rotations of all our compounds were opposite in sign from what is reported here since we started from (-)-carvone. Since almost all work in the literature was carried out with (+)-carvone we have reversed the signs in this report to avoid confusion.

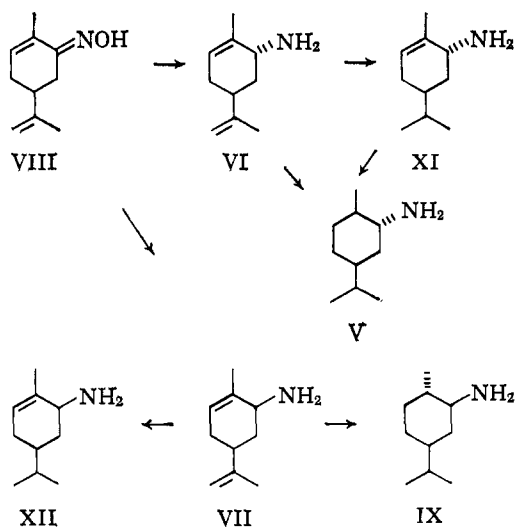
(11) H. Goldschmidt and A. Fischer [*Ber.*, **30**, 2069 (1897)] report m.p. 103°, [α]_D +177°, for the derivative of VI and m.p. 169°, [α]_D -92°, for the derivative of VII.

(12) E. Deussen and A. Hahn, *Ann.*, **369**, 60 (1909).



v.p.c.) were separated by fractional crystallization of their benzoyl derivatives. The benzoyl derivative of amine VII could also be prepared from the products of reduction of VIII with lithium aluminum hydride in tetrahydrofuran.

That (-)-*cis*-carvylamine does, in fact, have configuration VII was demonstrated by hydrogenation to the known^{1a,2a} (+)-carvomenthylamine (IX), benzoyl derivative m.p. 161-163°, [α]_D +40.5°, of established⁸ configuration. (+)-*trans*-Carvylamine is epimeric with (-)-*cis*-carvylamine and is therefore correctly represented by configuration VI. Its hydrogenation product, "(-)-isocarvomenthylamine," thus has configuration V; the alternative configuration X is excluded because of the origin of V from reduction of (-)-isocarvomenthone oxime (I) and also because configuration X has been conclusively assigned⁸ to another compound, (-)-neocarvomenthylamine, benzoyl derivative^{1a,2a} m.p. 129°, [α]_D -37.5°.



It is now clear that, because of the small size difference between methyl and isopropyl⁹ (which was not known to Bose³), coupled, possibly, with a "3-alkyl ketone effect,"¹³ (-)-isocarvomenthone oxime (I) may exist to a considerable extent in conformation Ia and thus it is not unreasonable that its reduction with sodium and ethanol produces V.

Partial hydrogenation of VI produces (+)-*trans*-carvotanacetylamine, XI, benzoyl derivative¹⁴ m.p. 95–97°, [α]_D +193°, whereas partial hydrogenation of VII produces (-)-*cis*-carvotanacetylamine, XII, benzoyl derivative¹⁴ m.p. 162°, [α]_D -85.5°, whose configurations are therefore proved to be as shown in the formulations. Compound XI had previously been correlated with V by hydrogenation of the respective tartrate.¹⁴

Although the configuration we have proved for (-)-isocarvomenthylamine is different from that assigned by Bose, we feel that the name for this compound should be retained, the prefix "iso" indicating that the 4-isopropyl group is *cis* to the 1-methyl group and the absence of the prefix "neo" indicating that the 2-amino group is *trans* to the 1-methyl group. The as yet unknown isomer corresponding to configuration II in which the functional group at C₂ is *cis* to the methyl at C₁ would thus be called neoisocarvomenthylamine.

According to Brewster's calculations,¹⁵ neoisocarvomenthylamine (II) in the conformation shown should have M_D -55° whereas isocarvomenthylamine should have M_D -55° in conformation Va and M_D 0° in conformation Vb. The actual molecular rotation^{1b} of -23° for V supports the configurational assignment, assuming that both conformations Va and Vb contribute appreciably.¹⁶

In the full paper we shall deal with the rotations of the unsaturated amines VI, VII, XI, and XII, the correlation of the amines with the corresponding alcohols, and the steric course of reduction of the carvomenthone oximes with lithium aluminum hydride.

(13) N. L. Allinger and L. A. Freiberg, *J. Am. Chem. Soc.*, **84**, 2201 (1962); see, however, B. Rickborn, *ibid.*, **84**, 2414 (1962). Little is known about the 3-alkylketone effect of groups larger than methyl.

(14) J. Read and G. Swann, *J. Chem. Soc.*, 239 (1937).

(15) J. H. Brewster, *J. Am. Chem. Soc.*, **81**, 5483 (1959); cf. E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp. 406–409.

(16) The argument is weakened because the observed rotation for the conformationally homogeneous carvomenthylamine, M_D +20°, is also less than the calculated, M_D +55°. Professor J. H. Brewster has indicated to the authors that better agreement might be expected using the hydrochlorides of the amines.

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The Absolute Configurations of the Carvomenthols

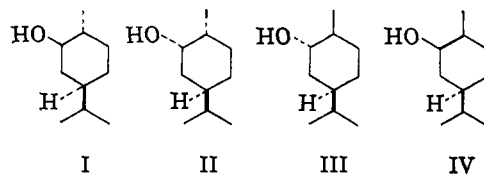
Sir:

We wish to cite an error in the stereochemical configurations assigned by Bose to the isomeric carvomenthols.¹ While the evidence for the configurations of carvomenthol (I) and neocarvomenthol (II) leaves

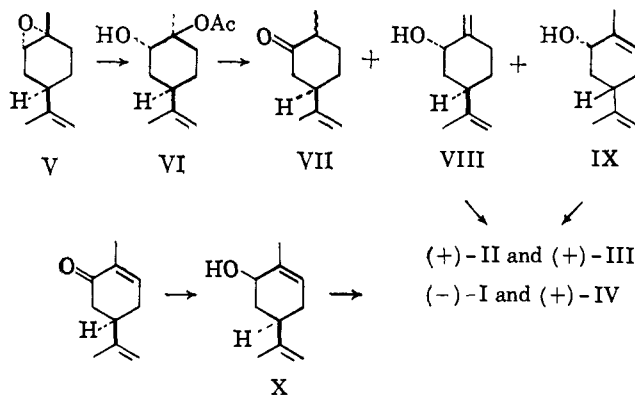
(1) A. K. Bose, *Experientia*, **8**, 458 (1952); the assignments of J. Simonsen and L. N. Owen, "The Terpenes," Vol. III, 2nd Ed., University Press, Cambridge, England, 1951, pp. 515–516, which were based on the work of R. G. Johnston and J. Read [*J. Chem. Soc.*, 1138 (1935)] are correct.

no doubt as to the stereochemistry of these isomers,² the configurations of isocarvomenthol (III) and neoisocarvomenthol (IV) have never been rigorously determined.

In connection with a study of the stereospecific ring opening of the (+)-limonene 1,2-oxides,³ (+)-*cis*-limonene 1,2-oxide (V, [α]_D^{24D} +36.00°)⁴ was treated with an acetic acid-sodium acetate solution to yield (+)-1-acetoxyn neodihydrocarveol (VI). Pyrolysis of this hydroxy acetate at 370° afforded a mixture of (+)-dihydrocarvoneisodihydrocarvone (VII, α ^{25D} +21.80°), (+)-*trans*-isocarveol (VIII, [α]_D^{25D} +82.00°), and (-)-*trans*-carveol (IX, [α]_D^{25D} -181.80°) which were separated by fractional distillation.⁵



Hydrogenation of (-)-*trans*-carveol (IX) gave a carvomenthol fraction consisting of 63% neocarvomenthol (II) and 37% isocarvomenthol (III), while (+)-*trans*-isocarveol (VIII) gave 24.5% neocarvomenthol (II) and 75.5% isocarvomenthol (III). A sample of (-)-*cis*-carveol (X)⁶ gave a mixture of 49% carvomenthol (I) and 51% neoisocarvomenthol (IV).^{7,8}



These facts are incompatible with the configurations of isocarvomenthol (IV) and neoisocarvomenthol (III) assigned by Bose.¹ There is, however, an obvious

(2) (a) J. T. Gresham, M.S. thesis, Emory University, 1961; (b) H. P. Orloff, *Chem. Rev.*, **54**, 375 (1954), and references therein.

(3) (a) J. C. Leffingwell, Ph.D. dissertation, Emory University, August, 1963. The application of the Fürst-Plattner rule to substituted monocyclic cyclohexene epoxides will be discussed in detail in another paper. See also: (b) J. A. Angyal, *Chem. Ind. (London)*, 1230 (1954); *Quart. Rev. (London)*, **11**, 212 (1957); (c) H. Kuczynski and K. Piatkowski, *Roczniki Chem.*, **33**, 299 (1959); *ibid.*, **33**, 311 (1959); (d) J. Sicher, F. Sipos, and M. Tichy, *Coll. Czech. Chem. Comm.*, **26**, 847 (1961); (e) H. Kuczynski and A. Zabza, *Bull. acad. polon. sci., Ser. sci. chim.*, **9**, 551 (1961); *Roczniki Chem.*, **35**, 1921 (1961); *ibid.*, **37**, 773 (1963).

(4) Preparation of this heretofore unreported isomer was effected by the sequence: (+)-*trans*-limonene 1,2-oxide → (+)-1-hydroxyneodihydrocarveyl → (-)-1-mesyln neodihydrocarveyl acetate → (+)-*cis*-limonene 1,2 oxide.

(5) The purity of each component was in all cases >95% (via v.p.c.); C, H, O analyses, derivatives, and infrared spectra were consistent for these structures.

(6) Prepared according to R. H. Reitsem, *J. Am. Chem. Soc.*, **75**, 1996 (1953).

(7) The hydrogenation experiments were carried out with PtO₂ in ethyl acetate. Analyses were by v.p.c. over a 20% Carbowax on firebrick substrate using authentic samples of the four isomeric carvomenthols as internal standards.

(8) Identical results were obtained from the carvotanacetols, prepared as above from (+)-*cis*-carvomenthene oxide.