Stereochemistry of Terpenes. IV. The Configuration of Some Amines[1]

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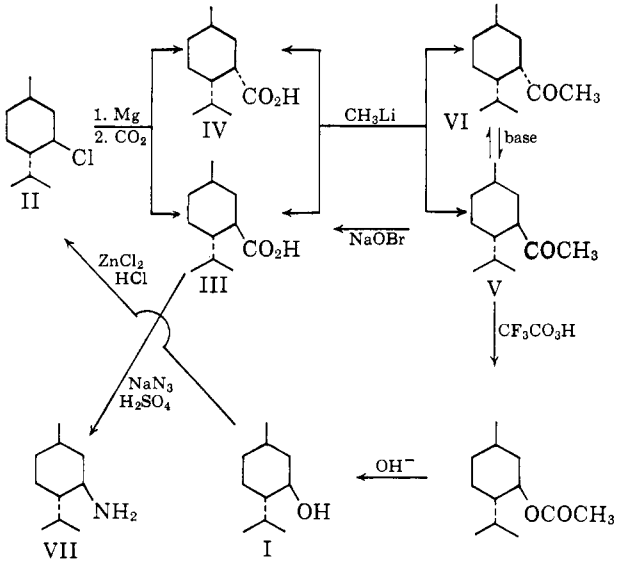
A direct stereochemical correlation between menthol and menthylamine has been established through a sequence of stereospecific reactions on a menthanecarboxylic acid. The configuration of neoisomenthylamine and a new compound, neoisopinocamphylamine, has been determined by their preparation from isomenthol and isopinocampheol, respectively, by reactions of known stereochemistry.

The stereochemistry of isomeric menthylamines was assigned by Read[2] on the basis that the optical rotation of their derivatives fitted the principle of superposition and that there was a regular pattern in the behavior of the amines on treatment with nitrous acid.[3] Sodium and alcohol reduction of (−)-menthone and the corresponding oxime leads predominantly to (−)-menthol and (−)-menthylamine, respectively. Conformational analysis[4] predicts analogous stereochemistry (equatorial —OH and —NH_2) for (−)-menthol and (−)-menthylamine. Similar arguments can be advanced for the stereochemistry of isomenthol and isomenthylamine. We wish to report here data that correlate more directly the absolute configuration of some terpene alcohols and amines.

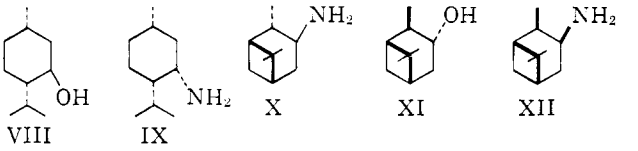
Carbonation of the Grignard reagent from (−)-menthyl chloride[5] (II) has been reported to give two epimeric acids (III and IV), one of which is a crystalline solid. We have carried out this Grignard reaction in tetrahydrofuran medium and analyzed the resulting mixture of acids by vapor phase chromatography of the corresponding methyl esters; the crystalline acid III and its epimer IV were obtained in the ratio of 2:1. Since the crystallization of III was a very slow process, the mixture of isomers was used in the next reaction. Treatment with methyllithium produced a mixture of methyl ketones V and VI with an epimer ratio of 3:1. Equilibration with base converted this mixture to V, the more stable isomer (acetyl side chain in the equatorial position). Hypobromite oxidation of V to menthanecarboxylic acid produced the isomer III exclusively. Since this oxidation proceeds without inversion, III and V must correspond to each other in configuration. Baeyer–Villiger oxidation of V followed by hydrolysis led to (−)-menthol. Schmidt reaction on III produced (−)-menthylamine. Since both the Baeyer–Villiger oxidation and the Schmidt reaction are known to proceed with retention of configuration, the absolute configuration of (−)-menthol (I), the carboxylic acid III, the methyl ketone V, and (−)-menthylamine (VII) must be as represented in col. 1.



We have recently described[6] a synthesis of axial amines by the following sequence.

Equatorial alcohol ⟶ equatorial tosylate $\xrightarrow[\text{in DMF}]{NaN_3}$ axial azide $\xrightarrow{2H}$ axial amine

The conversion of the tosylate to the azide is expected to proceed with Walden inversion[7] and this expectation was borne out by the preparation[6] of 3α-aminocholestane from 3β-cholestanol and (+)-neomenthylamine from (−)-menthol. Under similar reaction conditions we have prepared (+)-neoisomenthylamine from (+)-isomenthol (VIII). We can, therefore, write the absolute configuration IX for (+)-neoisomenthylamine.



The only pinocamphylamine that appears to have been reported[8] so far was obtained by the reduction of pinocamphone oxime with sodium and alcohol. Conformation analysis predicts the stereostructure X for this isomer. We have prepared an amine *via* the tosylate and azide from (+)-isopinocampheol (XI).[9] The tosylate was found to be quite unstable and the poor yield (8%) of the amine obtained from this tosylate was obviously due to extensive decomposition prior to the formation of the azide. The n.m.r. spectrum of the N-acetyl derivative of this amine showed it to be homogeneous. In the light of the observations made in the menthol series, the absolute configuration XII can be assigned to this amine which should be called (+)-neoisopinocamphylamine in keeping with the general usage regarding terpene nomenclature.

(1) Part III, A. K. Bose, *J. Org. Chem.*, **20**, 1010 (1955).
(2) J. Read and W. J. Grubb, *J. Chem. Soc.*, 313 (1934); N. L. McNiven and J. Read, *ibid.*, 153 (1952).
(3) Also see A. K. Bose, *Experientia*, **9**, 256 (1953); J. A. Mills, *J. Chem. Soc.*, 260 (1953).
(4) See, for example, H. S. Orloff, *Chem. Rev.*, **54**, 347 (1954).
(5) J. G. Smith and G. F. Wright, *J. Org. Chem.*, **17**, 1116 (1952).
(6) A. K. Bose, J. F. Kistner, and L. Farber, *ibid.*, **27**, 2925 (1962).
(7) P. Brewster, F. Hiron, E. D. Hughes, C. K. Ingold, and P. A. D. S. Rao, *Nature*, **166**, 178 (1950).
(8) O. Wallach and W. Rojahn, *Ann.*, **313**, 367 (1900); L. Ruzicka and S. Pontalti, *Helv. Chim. Acta*, **7**, 489 (1924).
(9) H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **81**, 247 (1959).

Experimental

All melting points were taken in capillary tubes and were uncorrected. Microanalyses were prepared by Schwarzkopf Microanalytical Laboratory, Woodside 77, New York, and Alfred Bernhardt, Mikroanalytisches Laboratorium im Max-Planck-Institut, Mülheim (Ruhr), West Germany. The optical rotatory dispersion studies were made with a Rudolph self-recording spectropolarimeter. Gas chromatographic studies were made with a Perkin–Elmer vapor fractometer using columns A (diisodecyl phthalate) and K (Carbowax 1500).

(−)-Menthyl Chloride (II).—Following the method described by Smith and Wright,[5] (−)-menthol was treated with the Lucas reagent to produce menthyl chloride, $n^{20}D$ 1.4615. Vapor phase chromatography (v.p.c.) indicated the material to be homogeneous.

***p*-Menthane-3-carboxylic Acids (III and IV).**—(−)-Menthyl chloride (20 g.) in 10 ml. of tetrahydrofuran was added over 30 min. to 5 g. of magnesium turnings and 20 ml. of tetrahydrofuran under nitrogen. The Grignard reaction was best initiated by the addition of a few pieces of magnesium that were vigorously reacting with ethyl bromide and a crystal of iodine in a separate vessel. After refluxing for a further hour, the liquid phase of the solution mixture was siphoned onto 200 g. of solid carbon dioxide. Following acidification with dilute hydrochloric acid, the products were extracted with ether. The acid fraction was separated by washing the ether layer with 5% sodium hydroxide solution. Acidification of the aqueous layer and extraction with ether gave 16 g. of an acid, A. V.p.c. of the methyl ester prepared from a sample of this acid with diazomethane showed the presence of the epimers III and IV in the ratio of 68:32. The acid mixture, A, crystallized partially on long standing; filtration and washing with hexane gave the solid isomer III, m.p. 62–65°, $[\alpha]^{20}D$ −46.5° (*c*, 1.46 in $CHCl_3$). The thiomorpholinamide derivative[10] of III, m.p. 111–113°, showed a negative Cotton effect.

Menthyl Methyl Ketones (V and VI).—A solution of 6.5 g. of the acid mixture A (see above) in 50 ml. of ether was added dropwise with stirring under nitrogen to a solution of methyllithium prepared from 3 g. of lithium in 100 ml. of ether. After standing overnight the solution was poured into ice–water and the ether layer separated. Removal of the solvent after drying over magnesium sulfate gave 4.8 g. of crude ketone, vapor phase chromatography ("K" column) of which showed the presence of both epimers V and VI in about 3:1 ratio. The O.R.D. curve in methanol had a negative Cotton effect with the extremum at 320 mμ. Acidification of the aqueous layer gave 1.7 g. of unchanged acid.

Equilibration of Methyl Menthyl Ketone Epimers V and VI.—Four grams of the above epimer mixture was equilibrated by refluxing with 40 ml. of 2% methanolic sodium hydroxide solution. Addition of water and extraction with ether followed by drying and removal of the solvent gave the epimer V, b.p. 68–69° (2 mm). V.p.c. indicated less than 2% of the isomer VI. The O.R.D. curve in methanol of V had a positive Cotton effect with the extremum at 303 mμ, $[\alpha]^{23}D$ −26.0° (*c*, 100), $[\alpha]^{25}D$ 1.4557. The 2,4-dinitrophenylhydrazone of V had m.p. 136–137° (from isopropyl alcohol).

Anal. Calcd. for $C_{18}H_{26}O_4N_4$: C, 59.12; H, 7.18; N, 15.5. Found: C, 59.78; H, 7.29; N, 15.25.

Hypobromite Oxidation of V.—A solution of sodium hypobromite from 1.2 g. of sodium hydroxide, 200 mg. of bromine and 10 ml. of water was added dropwise to 240 mg. of V in 10 ml. dioxane at 0°, and stirred for 2 hr. After standing overnight, 200 mg. of sodium bisulphite was added and the solution refluxed for 2 hr. The reaction mixture was poured into water and the neutral fraction extracted with ether. Acidification of the aqueous layer gave 110 mg. of an acid. V.p.c. of the methyl ester prepared by the addition of diazomethane in ether showed a single peak which coincided with the peak observed for the ester of the crystalline acid III.

Baeyer–Villiger Oxidation of V.—Trifluoroacetic anhydride (14 ml.) was added dropwise to a suspension of 2 ml. of 90% hydrogen peroxide[11] in 20 ml. of methylene chloride at 0°, and the resulting solution added slowly to 2.4 g. of V in 50 ml. of methylene chloride at 0°. After 0.5 hr., 24 g. of anhydrous dibasic sodium phosphate was added and refluxed for 2 hr. The mixture was filtered, the solvent evaporated, and the product distilled at 150° (bath temp.) (2 mm.), yield 2.0 g. By coincidence of peaks by v.p.c., the product was shown to be (−)-menthol acetate. Hydrolysis of 1.5 g. by refluxing in 5 ml. of 10% aqueous ethanolic potassium hydroxide for 2 hr. gave 1.1 g. of (−)-menthol, isolated by addition of water and extraction with ether followed by drying and removal of solvent. Its comparison with (−)-menthol using v.p.c. indicated that the two samples were identical. The 3,5-dinitrobenzoate had m.p. 152–153° [undepressed by admixture with an authentic sample of (−)-menthol 3,5-dinitrobenzoate], $[\alpha]^{20}D$ −79.3° (*c*, 1.6, $CHCl_3$).

(−)-Menthylamine.—One hundred and thirty milligrams of sodium azide was added in small portions to a stirred mixture of 166 mg. of the acid, 3 ml. of concentrated sulphuric acid, and 6 ml. of chloroform at 50–55°. After 0.5 hr. at this temperature, the mixture was diluted with ice–water and neutral materials removed by extraction with ether. Addition of excess sodium hydroxide solution liberated the free amine which was extracted into ether and dried over sodium hydroxide pellets. The solvent was removed, 2 ml. of acetic anhydride added, and the solution refluxed for 1 hr. Evaporation of the solvent under reduced pressure gave 109 mg. of N-acetyl (−)-menthylamine which was recrystallized from benzene; m.p. 145–146°, $[\alpha]^{21}D$ −84° (*c*, 0.8 in $CHCl_3$).

In a similar experiment 1 g. of III was converted to 0.8 g. of N-benzoyl-(−)-menthylamine, m.p. 157°, undepressed on admixture with an authentic sample.

(−)-Neoisomenthylamine Hydrochloride.—To 1.22 g. (3.9 mmoles) of (+)-isomenthyl *p*-toluenesulfonate[12] dissolved in a mixture of 30 ml. of dimethylformamide and 4.5 ml. of water was added 1.29 g. (20 mmoles) of sodium azide. The temperature was kept at 85° with stirring for 9 hr. The reaction mixture then was poured into 30 ml. of a saturated aqueous sodium chloride solution diluted with 3 ml. of water. It was then extracted with ether and the combined ether extracts were washed with the saturated sodium chloride solution and dried over magnesium sulfate.

To a suspension of 0.3 g. (7.9 mmoles) of lithium aluminum hydride in 50 ml. of absolute ether there was added, over a period of 30 min., the dried ether extract from above. The mixture was stirred at room temperature for 1 hr. and then refluxed for 1 hr. more. The excess lithium aluminum hydride was destroyed with moist ether followed by water and the solid material was filtered off. The organic layer was washed twice with a saturated sodium chloride solution and dried over anhydrous magnesium sulfate. Hydrogen chloride gas was passed into this ether solution and the mixture then was allowed to evaporate. After washing the resulting residue with hexane, 0.13 g. (17%) of white crystalline neoisomenthylamine hydrochloride was obtained.

Acetylation of neoisomenthylamine hydrochloride with acetic anhydride in a pyridine carbon tetrachloride solution yielded (−)-N-acetylneoisomenthylamine, m.p. 99–100.5° (lit.,[13] 99–100°).

Anal. Calcd. for $C_{12}H_{23}NO$: N, 7.10. Found: N, 7.07.

Neoisopinacocamphylamine Hydrochloride.—To 6.17 g. (0.020 mole) of isopinocamphyl *p*-toluenesulfonate[14] dissolved in a mixture of 125 ml. of N,N-dimethylformamide and 21 ml. of water was added 6.50 g. (0.1 mole) of sodium azide. The mixture was stirred and kept at a temperature of 60° for 6 hr. The reaction mixture then was poured into water. It was extracted with ether and the combined ether extracts were washed with the saturated sodium chloride solution and dried over anhydrous magnesium sulfate.

To a suspension of 1.52 g. (0.04 mole) of lithium aluminum hydride in 50 ml. of absolute ether there was added, over a period of 30 min., the dried ether extract from above. The mixture was stirred at room temperature for 1 hr. and then refluxed for 1 hr. more. The excess lithium aluminum hydride was destroyed with moist ether followed by water and the solid material was filtered off. The organic layer was washed twice with a 3 *N* sodium hydroxide solution and dried over anhydrous magnesium sulfate. The solution was reduced in volume and to it was added a solution of hydrogen chloride gas in ether. The

(10) C. Djerassi and K. Undheim, *J. Am. Chem. Soc.*, **82**, 5755 (1960).

(11) W. D. Emmons and G. B. Lucas, *ibid.*, **77**, 2287 (1955).

(12) W. Hückel and H. Niggemeyer, *Ber.*, **72B**, 1354 (1939).

(13) J. L. Simonsen, "The Terpenes," Vol. I, 2nd ed., Cambridge University Press, Cambridge, England, 1953, p. 245.

(14) Reported as a liquid by H. Schmidt, *Ber.*, **77**, 544 (1944). Isopinocamphyl *p*-toluenesulfonate, which was prepared by treating (+)-isopinocampheol with *p*-toluenesulfonyl chloride in pyridine, is an unstable crystalline material and was used immediately after preparation.

solid, white neoisopinocamphylamine hydrochloride, 0.31 g. (8.1%) was obtained.

Acetylation of neoisopinocamphylamine hydrochloride with acetic anhydride in the presence of sodium hydroxide solution gave (+)-N-acetylneoisopinocamphylamine, m.p. 148.5–149.5°, $[\alpha]^{28}D$ +50.8° (chloroform *c*, 1.51).

Anal. Calcd. for $C_{12}H_{21}ON$: C, 73.79; H, 10.84; N, 7.17. Found: C, 74.26; H, 10.87; N, 7.54.

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Alkylbenzenes. IX. Equilibration of the α- and β-Carbon Atoms in C^{14}-Labeled *n*-Propylbenzenes by Lewis Acid Catalysts[1]

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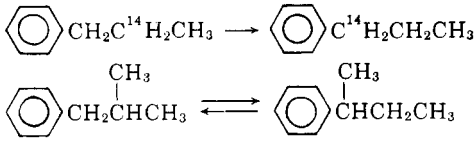
Multiple treatments with fresh aluminum chloride of *n*-propylbenzene labeled in either the α- or β-position with C^{14} led to complete equilibration of the isotopic carbon between the α- and β-positions of the side chain of recovered *n*-propylbenzene; no appreciable amount of the isotope was found in the γ-position. The effectiveness of other Lewis acid catalysts for rearrangement of C^{14}-labeled *n*-propylbenzene was tested; hydrogen bromide–aluminum bromide produced 44% rearrangement from the α- to the β-position in one treatment.

The aluminum chloride-induced rearrangement of *n*-propyl-β-C^{14}-benzene was reported to result in the appearance of up to 31% of the C^{14} in the α-position of the normal side chain, while none was found in the γ-position.[3] Subsequently it was demonstrated that either isobutyl- or *sec*-butylbenzene is converted under the same conditions into a mixture containing a 2:1 proportion of isobutyl- and *sec*-butylbenzene, respectively.[4] In a sense, the butylbenzene isomers may be considered to be β- and α-methyl-labeled propylbenzenes, so that the similarity in the rearrangement reactions is obvious.



The 2:1 "equilibrium" proportion of isobutyl- and *sec*-butylbenzene produced from either of these butylbenzene isomers is probably a result of several factors; *e.g.*, the relative thermodynamic stability of the two isomers[4,5] and their relative susceptibilities toward dealkylation and fragmentation reactions.[6]

However, α- and β-C^{14}-labeled *n*-propylbenzene molecules are chemically identical, and one would expect that the isotopic rearrangement of *n*-propyl-β-C^{14}-benzene should result in a 50:50 distribution of C^{14} between the α- and β-carbon atoms, since the γ-carbon atom is apparently not involved.[3] It occurred to us that a possible explanation of the observed incomplete rearrangement lay in deactivation of the catalyst by the di-, tri-, and polypropylbenzenes formed by disproportionation reactions which are concurrent with the rearrangement. A simple experimental test of this theory appeared to be multiple treatments with fresh catalyst; *i.e.*, α- or β-C^{14}-labeled *n*-propylbenzene would be treated with catalyst, the monopropylbenzene separated from benzene, dipropylbenzene and higher disproportionation products, degraded, and radioassayed to determine the extent of isotopic rearrangement. This recovered, partially rearranged *n*-propylbenzene would then be subjected to treatment with fresh catalyst and the separation, degradation, and radioassay of recovered *n*-propylbenzene repeated. If the theory of catalyst deactivation were correct, repetition of these procedures should result in a 50:50 distribution of C^{14} between the α- and β-carbon atoms of the side chain.

This paper describes results of such experiments and of certain other related experiments.

Discussion of Results

In previous papers we suggested two mechanisms for the rearrangement of *n*-propyl-β-C^{14}-benzene to *n*-propyl-α-C^{14}-benzene,[3,7] and Nenitzescu and coworkers[5] proposed a third which differed slightly from our second mechanism. Each of the steps in all of these mechanisms are assumed to be reversible, and hence we expected that an equal distribution of C^{14} between the α- and β-carbon atoms should be approached from starting material labeled in either position. To test the validity of these assumptions we synthesized both *n*-propyl-α-C^{14}-benzene and *n*-propyl-β-C^{14}-benzene.

Two syntheses of *n*-propyl-α-C^{14}-benzene utilizing (a) sodium cyanide-C^{14} and (b) barium carbonate-C^{14} as sources of the isotopic label are outlined in Fig. 1. A method different from that used in the earlier work[3] was used for the synthesis of *n*-propyl-β-C^{14}-benzene; it is outlined in Fig. 2.

Multiple Rearrangements of *n*-Propyl-α-C^{14}-benzene.—Treatment of *n*-propyl-α-C^{14}-benzene with aluminum chloride at 100° for 6.5 hours in three consecutive stages is outlined in Fig. 3. The procedure

(1) A preliminary report of some of the results described fully here was given in *Chem. Ind.* (London), 1557 (1958).

(2) Taken from the Ph.D. thesis of James E. Douglass, The University of Texas, 1959. Procter and Gamble Co. Fellow, 1957–1958; University of Kentucky, Lexington, Ky.

(3) (a) R. M. Roberts and S. G. Brandenberger, *Chem. Ind.* (London), 227 (1955); (b) R. M. Roberts and S. G. Brandenberger, *J. Am. Chem. Soc.* **79**, 5484 (1957).

(4) R. M. Roberts, Y. W. Han, C. H. Schmid, and D. A. Davis, *ibid.*, **81**, 640 (1959).

(5) C. D. Nenitzescu, I. Necsoiu, A. Glatz, and M. Zalman, *Chem. Ber.*, **92**, 10 (1959).

(6) These reactions will be the subject of a subsequent paper.

(7) J. E. Douglass and R. M. Roberts, *Chem. Ind.* (London), 926 (1959).