# CIRCULAR DICHROISM AND CONFIGURATION OF (−)-1-METHYL-1,2,3,4,TETRAHYDROISOQUINOLINE

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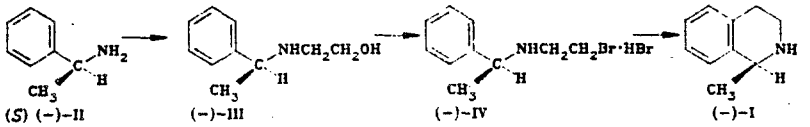
UDC 541.63:547.833:543.422

In the CD (circular dichroism) spectra of (−)-1-methyl-1,2,3,4,tetrahydroisoquinoline, three CE (Cotton effects) are observed in the 300-200 nm region that are due to the absorption bands of the aromatic chromophore. The synthesis of this substance from (S)(−)-α-phenylethylamine and the CD spectra confirm its (S)-configuration.

The tetrahydroisoquinoline nucleus enters into the composition of many alkaloids that have valuable physiological properties. Many of its derivatives are basic to medicinal preparation [1]. Tetrahydroisoquinolines with a substituent in the 1 position can exist in optically active form. There are data in the literature concerning the CD of a number of complex systems containing the tetrahydroisoquinoline fragment. These data allow one to establish the configuration of many compounds [2-4]. However, the chiroptic properties of the simplest, optically active 1-methyl-1,2,3,4-tetrahydroisoquinoline (I) have hardly been studied. Only in an article on the application of semiempirical regional rules for tetrahydroisoquinoline systems [5] is there a reference to unpublished data on the CE of 1-methyl-1,2,3,4-tetrahydroisoquinoline in the 272 and 220 nm region.

Optically active I was first obtained in 1929 [6] by resolving the racemic amine with the aid of D-tartaric acid. Craig, et al. [7] have recently described the asymmetric synthesis of (−)-I in high optical purity (>90%) by the alkylation of chiral N-formamide derivatives of tetrahydroisoquinoline at the $C_{(1)}$ atom by the action of lithium diisopropylamide and and then MeI. However, in this case, it is necessary to have already prepared the tetrahydroisoquinoline system, which is usually obtained from a β-phenylethylamine derivative.

For a long time, attempts to use benzylamine to obtain tetrahydroisoquinolines were not successful; only in 1973 was the synthesis of unsubstituted and 6-chlorosubstituted tetrahydroisoquinoline from the corresponding benzylamines described [8]. We used this method to obtain compound I, taking as the starting substance α-methylbenzylamine (α-phenylethylamine) [9], which is readily available in both enantiomorphic forms.




(S) (−)-II (−)-III (−)-IV (−)-I

From amine (−)-II, we obtained (−)-N-(2-hydroxythyl)-α-phenylethylamine [(−)-III] [10]. We carried out the replacement of the hydroxyl group by a bromine by two methods: by boiling aminoalcohol III with concentrated hydrobromic acid or by heating it with thionyl bromide. The reaction takes place with a greater yield in the second case and leads to a purer substance. Moreover, the hydrobromide of (−)-(2-bromoethyl)-α-phenylethylamine [(−)-IV] obtained with the use of thionyl bromide can be used in the subsequent cyclization without further purification. We cyclized hydrobromide IV by the action of anhydrous $AlCl_3$ at 140-145°C because it was shown that at the temperatures given in [8] (120-130°C), the reaction does not go. The yield amounted to 60%. When the temperature is increased, there is considerable tar formation and the yield falls to 20%. In carrying out the cyclization, we used a greater quantity of solvent (decalin) than indicated in [8] in order to overcome the the intermolecular interactions that lead to polymer. The overall yield of compound (−)-I calculated from the initial (−)-α-phenylethylamine came to ~ 40%.

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 0009-3122/87/2309-0990$12.50 

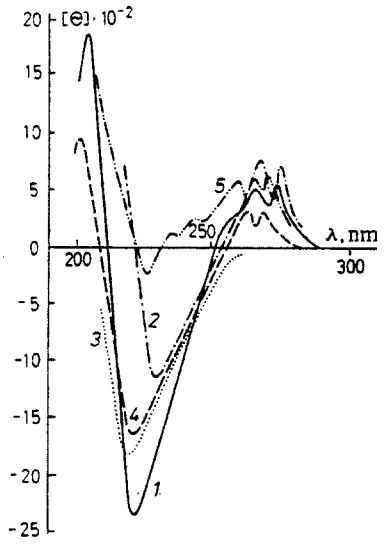


Fig. 1. The CD spectra of compounds (−)-I (1-3) and (S)(−)-α-phenylethylamine (4, 5): 1, 4) in alcohol; 2, 5) in isooctane; 3) in alcohol with added HCl

The advantages of the scheme we have developed compared to the method in [6] are obvious. The synthesis is carried out in three steps (instead of four), obviating the most laborious step, the resolution of racemic compound I, during which the greatest loss of material occurs. The overall yield of optically active 1-methyl-1,2,3,4-tetrahydroisoquinoline is not mentioned in [6], but from the literature data on the separate steps, it can be estimated as not greater than 20%.

From a GLC study of N-trifluoroacetyl-(S)-propyl derivatives of various amines, including cyclic amines, [11], it follows that compound (−)-I has an S configuration. Our synthesis of this compound from (S)(−)-α-phenylethylamine is direct chemical confirmation of its S configuration inasmuch as all of the reactions take place without involving the asymmetric center.

Measurement of the CD of tetrahydroisoquinoline (−)-I showed the presence of three CE in the 300-200 nm region (Fig. 1): a complex positive CE in the 280-260 nm region due to the $^1L_B$ absorption band of the aromatic chromophore; a negative CE in the 230-220 nm region; and a positive CE in the 200 nm region. The CE at 230-220 nm is solvent dependent, its value in isooctane being significantly less than in alcohol and it is bathochromically shifted with respect to the CE found in alcohol. The shortwave-length CR is probably due to $^1L_a$ and $^1L_{2u}$ transitions in the aromatic chromophore. The CE in the 220 nm region contains a contribution from the $n \rightarrow \sigma^*$ transition in the amino group since this CE is diminished on acidification of the solution.

Comparison of the CD spectra of compounds (−)-I and (−)-α-phenylethylamine showed that they are analogous (Fig. 1). This is one more confirmation that both amines have the same configuration. The small increase in the CE in compound (−)-I compared to amine (−)-II may be due to the attachment of the aromatic chromophore in the cyclic, tetrahydroisoquinoline system.

## EXPERIMENTAL SECTION

The CD were measured on a JASCO J-20 automatic spectropolarimeter in cuvettes with a 1 and 10 mm pathlength.

(−)-N-(2-Hydroxyethyl)-α-phenylethylamine (III) was obtained by the procedure in [10], $T_{bp}$ 144°C (5 mm), $[\alpha]_D$ −40.7° (alcohol, c 0.4).

Hydrobromide (−)-N-(2-Bromethyl)-α-phenylethylamine (IV). A. A midture of 0.13 mole of (−)-N-(2-hydroxyethyl)-α-phenylethylamine and 0.64 mole of hydrobromic acid (d 1.5) is boiled for 12 hours and evaporated down. The residue is recrystallized 3-4 times from the minimum amount of water. Yield 17 g (~42%). $T_{mp}$ 196-198°C.

B. 0.32 mole of thionyl bromide is added dropwise to 0.23 mole of compound III in 50 ml of absolute benzene. The mixture is heated for three hours on a water bath. When the solution cools, a yellow precipitate forms which is filtered off and purified by reprecipitation from methanol solution with absolute ether. Yield 66 g (82%), $T_{mp}$ 205-206°C, $[\alpha]_D$

−23.5° (alcohol, c 0.5). Found: C, 39.1; H, 5.1%. $C_{10}H_{14}BrN \cdot HBr$. Calculated: C, 38.9; H, 4.9]. Rotatory power in alcohol (c 0.045), [M]° (λ, nm): 510 (300), 547 (290), 615 (285), 649 (275), 479 (268), 958 (265), 822 (262), 1199 (258), 1026 (255), 1335 (250), 2550 (230).

(−)-1-Methyl-1,2,3,4-tetrahydroisoquinoline (I). A mixture of 0.04 mole of compound IV, 0.09 mole of $AlCl_3$, and 150 ml of decaline distilled from over sodium is heated for three hours at 145-150°C. After the end of the heating, the reaction mixture is decomposed with ice and conc. HCl, the decaline layer is separated, the aqueous layer is extracted with benzene or ether (5 × 50 ml), then made alkaline with NaOH and extracted with ether (5 × 50 ml). The ether extract is dried with NaOH, the ether distilled off, and the residue redistilled. Yield 2.9 g (54%), $T_{bp}$ 90°C (2 mm), $[\alpha]_D^{20}$ −76.1° (alcohol, c 0.1). Rotatory power in isooctane (c 0.1), [M]° (λ, nm): −375 (300), −91 (274), −524 (270), −205 (268), −1140 (249), 0 (230), 410 (225). CD in isooctane (c 0.5), [θ]° (λ, nm): 774 (273), 463 (270), 873 (266); (c 0.05): −1170 (30), 615 (218).

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# MASS SPECTROSCOPIC STUDY OF 9-AMINO- AND 9-ALKYL(DIALKYL, SPIRO)-1- AND 4-AZAFLUORENES


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UDC 543.51:547.678.3'83



Elimination of a substituent from the 9-position appears to be the main pathway for decomposition of 9-amino-4-azafluorenes. An amine type fragmentation pattern has been observed as well. Decomposition of 9-spiro-4-azafluorenes occurs via cleavage of the radical bound to the three-membered ring. 9-Alkyl-(dialkyl)-1- and 4-azafluorenes also readily lose a substituent in position 9. The observed pathways and principles allow one to determine the nature of the substituent in the 9-position and also to differentiate 1-azafluorenes from 4-azafluorenes.


We have previously developed methods for the synthesis of, and have studied the properties and chemical reactions of, 9-amino- and 9-alkyl(dialkyl, spiro)-1- and 4-azafluorenes [1-4]. The presence of functional substituents in these molecules makes them not only of synthetic importance, but also of practical utility. In analogy with fluorene derivatives


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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1241-1246, September, 1987. Original article submitted March 24, 1986; revision submitted December 22, 1986.




0009-3122/87/2309-0992$12.50