Formation of Optically Active Compounds under Achiral Synthetic Conditions

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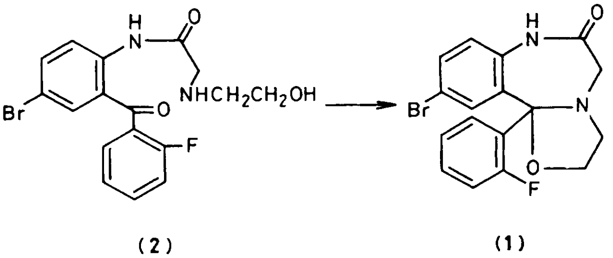
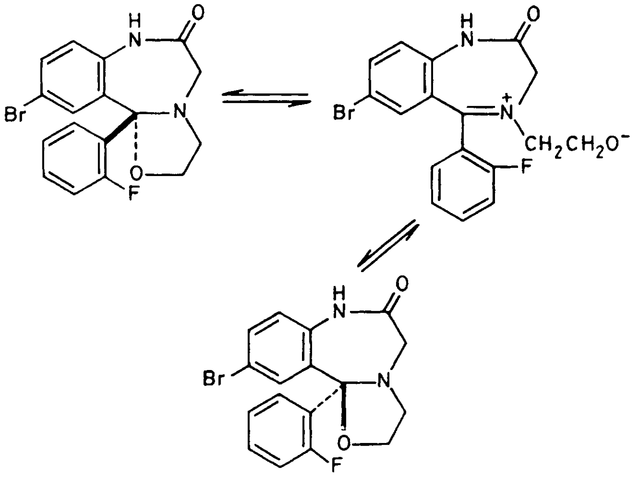
An unusual and simple method of obtaining enantiomers under chemically and physically achiral conditions has been found in which preferential crystallization accompanied second order asymmetric transformation.

The synthesis of (*RS*)-10-bromo-11b-(*o*-fluorophenyl)-2,3,7,11b-tetrahydro-oxazolo[3,2-*d*][1,4]benzodiazepin-6(5*H*)-one (**1**) by intramolecular condensation of 2-(2-hydroxyethylamino)acetamido-5-bromo-2′-fluorobenzophenone (**2**) has recently been reported (Scheme 1).[1] We found that one enantiomer of (**1**) was obtained in fairly good yield with a high degree of optical activity, when the procedure was conducted as follows: the benzophenone derivative (**2**) (21.8 g, 55 mmol) was dissolved in methanol (174 ml) containing glacial acetic acid (0.65 ml, 11 mmol) and the solution was refluxed for 20 h. After being cooled to room temperature, the crystalline precipitate was collected, washed with methanol (50 ml), and dried in a desiccator to constant weight to afford the oxazolobenzodiazepinone (14.8 g, 72.1%) as prisms of m.p. 177.5—178.5 °C. The product showed a specific rotation of −318.3° equivalent to $[M]_D^{25}$ −1200.5° when measured in dioxane (*c* 0.2%) at 25 °C. The filtrate and methanol wash were combined and concentrated to one quarter of the initial volume to give



(**2**) (**1**)

Scheme 1



Scheme 2

a second crop (3.36 g, 16.2%); $[\alpha]_D^{25}$ $-218.3°$ (c 0.2%, dioxane). The experiment was repeated several times and the product from each run gave optically active solutions when dissolved in dioxane; these were sometimes dextrorotatory and sometimes levorotatory. Absolute values of the specific rotations at 25 °C varied between 307.7 and 326.6°.

The optically active crystals were dissolved in methanol with or without acetic acid and the optical rotation of the resulting solutions was measured. The plane of polarized light was not rotated. The racemization probably proceeds *via* a quarternary iminium ion as shown in Scheme 2.

These observations suggest that absolute asymmetric synthesis is not involved in the condensation process of (**2**) to (**1**). The crystallization process was therefore investigated. One enantiomer of (**1**) was dissolved in methanol by heating and the solution (5%) was boiled for 5 min, then rapidly chilled in dry ice–methanol to precipitate crystals; $[\alpha]_D^{25}$ 0° in dioxane. In these experiments rapid chilling invariably resulted in the formation of a racemic modification. A similarly prepared 5% methanolic solution of the racemic modification was boiled for 30 min in a vessel of capacity 1.3 times the volume of the solution. The vessel was sealed with a stopper, then maintained in a thermostat at 40 °C for three days. During this period crystals appeared; the vessel was then cooled slowly to room temperature.

A dioxane solution (c 2%) of the crystals collected showed a high degree of optical rotation, either dextrorotatory or levorotatory, *e.g.* $[\alpha]_D^{25}$ $+181.1$, $+241.9$, $+226.4$, and $-177.1°$; the corresponding yields were 69.5, 55.2, 49.0, and 58.0%. The mother liquors showed a specific rotation of 0°, without exception, indicating the fast equilibration of both enantiomers. Analogous results were obtained in similar experiments where a sealed glass tube was used to avoid the influence of the environment as much as possible. An *X*-ray analysis was carried out on the optically active crystals obtained by this process.

Crystal data: $C_{17}H_{14}BrFN_2O_2$, space group $P2_12_12_1$, $Z = 4$, $a = 10.333(3)$, $b = 7.229(2)$, $c = 21.287(6)$ Å. As there is no centre of symmetry in the crystal and one molecule in the asymmetric unit cell, only one enantiomer should exist. The crystal structure was solved by the heavy atom method and the current R factor is 0.056 for 1444 reflections measured in the range $2\theta = 55°$ with monochromated Mo-K_α radiation.[†] The two benzene rings are almost perpendicular to each other and the F atom is located between two N atoms at distances of 2.959 and 3.079 Å.

It is possible that resolution may occur by seeding of the same enantiomer existing as an undetectable impurity in the starting material derived from one enantiomer by racemization. However, this was shown to be incorrect by introducing a sample of the same crop to both enantiomers.

These observations indicate that the crystallization process is governed by second order asymmetric transformation. The formation of the optically active product in the synthesis may be interpreted in the same manner; that is, one enantiomer crystallizes in preference to the other owing to spontaneous nucleation, the mother liquor becoming racemic again by equilibration. By repeating this process, crystals are accumulated.

An analogous phenomenon occurring in the recrystallization of a racemic modification has been reported in the literature,[2] although the data may not be reproducible.

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References

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2 E. Havinga, *Biochem. Biophys. Acta*, 1954, **13**, 171.

[†] The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Rd., Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.