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Faculty of Chemistry and Pharmacy, University of Regensburg,
Postfach 397, D-8400 Regensburg, Germany

Intramolecular von-Braun-Reaction: Evidence of Inversion

By
S. Prior and **W. Wiegrebe**

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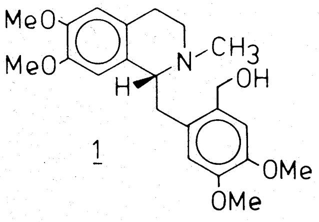
Recently, Bremner[1] and Prior[2], respectively, have published experiments concerning the intramolecular participation of nucleophilic moieties in the course of the BrCN-degradation of amines. The racemate of the benzylisoquinoline **1,** e. g., is converted to the 3-phenylisochromane **2**, R = CN. – This paper refers to stereochemical aspects of this reaction: we have shown[3] that ethylchloroformate converts R–**1** to the phenylisochromane S–**2**, R = CO–OEt, which was proven by O_3-degradation of its oxidation product **3** to S-malic acid (**4**, R = H). A similar inversion was expected to occur in the course of the reaction of R–**1** with BrCN to optically active **2**, R = CN. Contrarily to the O_3-degradation of the phenylisochromanone **3** this degradation procedure should give rise to chiral O-carboxymethylmalic acid (**4**, R = CH_2–COOH) besides other degradation products. In order to facilitate the search of this key molecule we tried to synthesize it by condensation of malic acid dimethylester with bromo-or iodoacetic acid methylester, but all these reactions failed under various basic conditions (Ag_2O, NaH, DIPEA, Na^0, TlOEt[4]) or led to fumaric acid dimethylester. Unexpectedly we were able to isolate S-malic acid **4**, R = H besides 1,3-dimethyl-imidazolidine-2,4,5-trione[5] from the ozonolysis of **2**, R = CN, so proving an inversion mechanism for this intramolecular von Braun-reaction.



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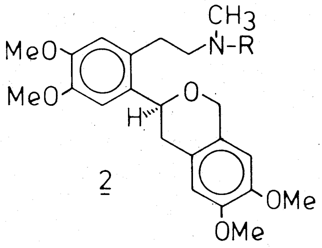

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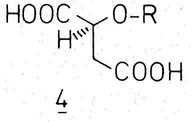

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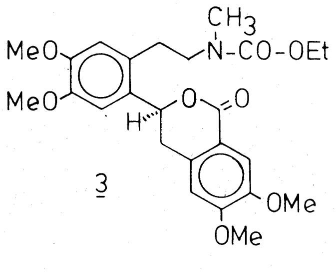

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Experimental Part

Preparation of S−**2**, R = CN.

The isochromane S−**2**, R = CN was synthesized from R−**1**[6] ($[\alpha]^{365}_{D} = -69°$ (Ethanol)) according to ref. 2.

Ozonolysis of S−**2**, R = CN to 1,3-dimethyl-imidazolidine-2,4,5-trione and S-malic acid **4**.

Ozonized oxygen (9 l./hr.) was passed through a solution of 2.0 g (4.8 mmol) S−**2**, R = CN in 100 ml glacial acetic acid for 12 hrs. at O^0. 8 ml H_2O_2 were added and the mixure was kept for 48 hrs. at room temperature. After addition of 40 ml water the solution was gently heated with Pd/charcoal (10 %) until the gas evolution seized. After filtration oxalic acid was precipitated by addition of calcium acetate. After filtration the solvent was removed in vacuo. The oily residue was dissolved in 100 ml methanol/water (9 : 1) and treated with an excess of ethereal diazomethane at room temperature. – The solvents were destilled off and the remaining oil was chromatographed (SiO_2; chloroform/ether 8 + 2):

1. fraction (rf 0.5): 0.03 g 1,3-dimethyl-imidazolidine-2,4,5-trione, colourless crystals, mp. 151° (lit.[5] 150°),

2. fraction (rf 0.3): oil, which was purified by destillation in vacuo (0.05 mm): 0.05 g S-**4**-dimethylester. The identity was proven by ^1H-NMR and MS, $\alpha^{20}_{D} = -0.038$; c = 3.2; acetone[7]. According to GC the oily material was contaminated by traces of oxalic acid dimethylester. Therefore, we didn't calculate the specific rotation.

Summary

An inversion mechanism is proven for the reaction of the benzylisoquinoline **1** with BrCN to the phenylisochromane **2**, R = CN.

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