Synthesis and Absolute Configuration of 2-Alkyl-chroman-4-spiro -hydantoin Derivatives

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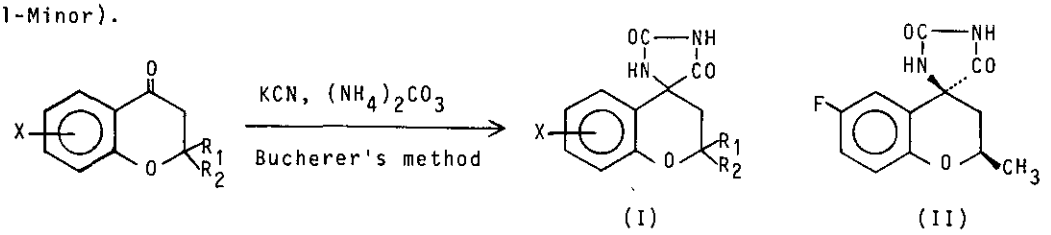
2-Substituted chroman-4-spiro-hydantoin derivatives (I) were synthesized from 4-chromanones by Bucherer's method. Among the hydantoins synthesized 2-monoalkyl derivatives (R_1:alkyl, R_2:H) showed strong inhibitory activity against aldose reductase and showed the possibility as the remedy for diabetic complications, e.g. neuropathy and cataract.

Thus, 6-fluoro-2-methyl-4-chromanone afforded two diastereomeric hydantoins in the ratio of 85:15. The predominant diastereomer (dl-Major) was optically resolved via the salt with methyl cinchonidium hydroxide. d-Major (II) was most active against aldose reductase among four isomers (d-Major, l-Major, d-Minor, l-Minor).



(I) (II)

The absolute configuration of these diastereomers was explored. From ^{1}H-NMR and X-ray diffraction studies, it was shown that 2-methyl group was equatorial. Analyzing the $^3J_{CH}$ coupling between 4'-carbonyl carbon and 3-methylene protons, the configuration of two diastereomers was assigned as follows: the major compounds (II) were RS, SR type and the minor compounds were RR, SS type. The NOE and other NMR experiments gave the same interproton distances as those found in the crystal, showing that the conformation of crystal form holds true in solution.