

This method was successfully applied to the assay of glycine in uric acid hydrolyzates¹⁾ and in plasma samples,⁴⁾ threonine in casamino acid¹⁾ and pantothenic acid in yeast extract,¹⁾ respectively.

Analysis of other amino acids and vitamins by this method is now in progress and the detail paper will be presented in the near future.

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- 4) T. Aikawa, H. Matsutaka, H. Yamamoto, T. Okuda, E. Ishikawa, T. Kawano, and E. Matsumura, *J. Biochem.*, **74**, 1003 (1973).

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Synthesis of 5-endo-Benzoyloxy-N-[amino(lower)alkyl]bicyclo[2.2.1]heptane-2,3-di-endo-carboxylic Acid Imides as Potential Antiarrhythmia Agents

A series of 5-endo-benzoyloxy-N-[amino(lower)alkyl]bicyclo[2.2.1]heptane-2,3-di-endo-carboxylic acid imides (**1**) have been synthesized and found to possess unique pharmacological activity as antiarrhythmia agents. An example of such a compound possessing excellent activity is 5-endo-benzoyloxy-N-(3-dimethylaminopropyl)bicyclo[2.2.1]heptane-2,3-di-endo-carboxylic acid imide (**1**: Ar=C₆H₅, R=CH₃, n=3) hydrochloride.

5-endo-Hydroxybicyclo[2.2.1]heptane-2,3-di-endo-carboxylic acid γ -lactone¹⁾ (**2**) was obtained by the acid-catalyzed lactonization of endo- or exo-*cis*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride, but preferably the endo-*cis* isomer.

2: mp 200° (lit.¹ 203°). IR $\frac{\text{KBr}}{\text{max}}$ cm⁻¹: 1770 (γ -lactone), 1690 (COOH). NMR (CDCl₃) δ : 1.33 (d,d C³H, $J_{2,3}$ =5.0 Hz, $J_{3,4}$ =2.0 Hz); 1.49 (d,t C²H, $J_{2,3}$ =5.0 Hz, $J_{1,2}$ =1.5 Hz, $J_{2,6\text{exo}}$ =2.0 Hz). The coupling constants for C²H and C³H indicated that they are exo.

2 was treated with acetyl chloride or phosphorous trichloride and then heated with alkyl-enediamine [NH₂(CH₂)_nNR₂] to give 5-endo-hydroxy-N-[amino(lower)alkyl]bicyclo[2.2.1]heptane-2,3-di-endo-carboxylic acid imides (**3**). Acylation of **3** with benzoyl halide gave **1**.

(**3**: R=CH₃, n=3): Colorless plates, mp 154°. *Anal.* Calcd. for C₁₄H₂₂O₃N₂·1/3H₂O: C, 61.76; H, 8.45; N, 10.29. Found: C, 61.93; H, 8.26; N, 10.40.

(**1**: Ar=C₆H₅, R=CH₃, n=3)·HCl: Colorless plates (hygroscopic), mp 239°. *Anal.* Calcd. for C₂₁H₂₆O₄N₂·HCl·1/3H₂O: C, 61.07; H, 6.83; N, 6.95. Found: C, 60.63; H, 6.88; N, 7.33. Nuclear magnetic resonance (free base in CDCl₃) δ : 8.0—7.3 (5H, C₆H₅), 5.17 (1H, C⁵H, broad d,t $J_{5,6\text{endo}}$ = $J_{4,5}$ =4.5 Hz, $J_{5,6\text{exo}}$ =10.5 Hz), 3.6—3.1 (5H, includes C²H, C³H, C⁴H, and CO₂NCH₂), 2.6—1.9 (9H, includes C⁷H₂, C⁶H_{endo}, and the remaining side chain CH₂). The coupling constants for C⁵H indicated, from Jackman and Sternhell,²⁾ that C⁵H is exo.

1) K. Alder, G. Stein, F.V. Buddenbrock, W. Eckardt, W. Frercks, and S. Schneider, *Ann.*, **514**, 1 (1934).

2) "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, 1969, p. 289.

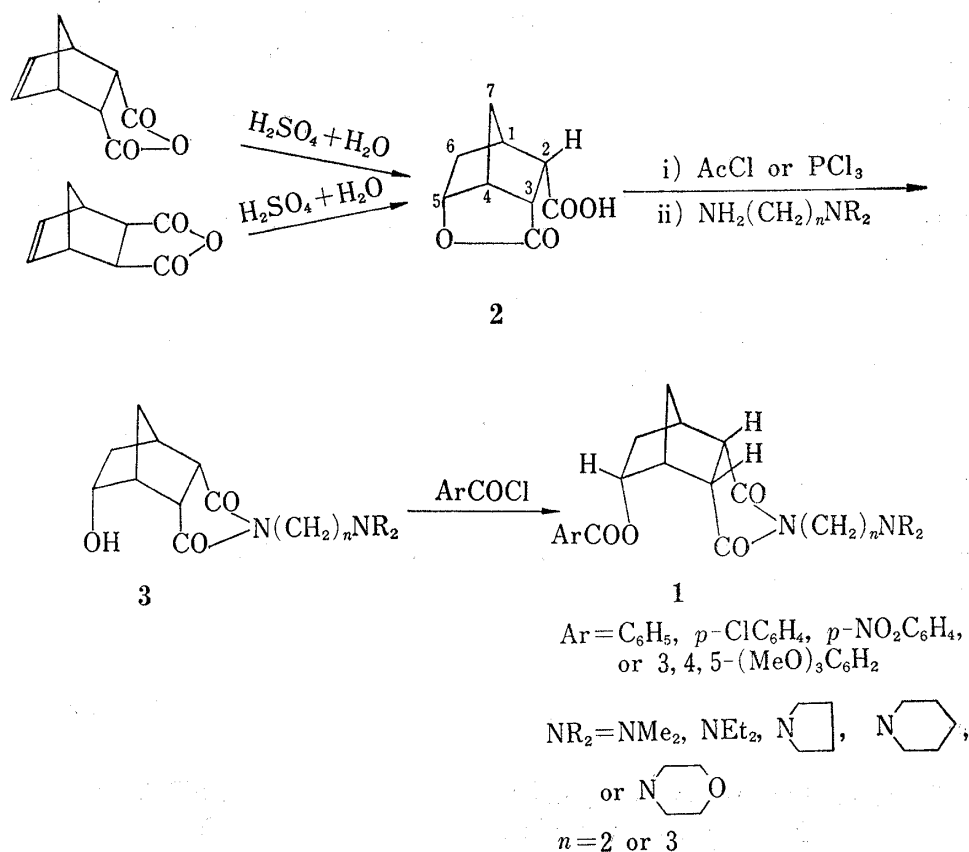


Chart 1

The use of Eu(fod)₃ in the CDCl₃ spectrum provided adequate separation for the C²H and C³H signal. Both the C²H and C³H exhibited couplings of 10 Hz and 4.5 Hz; thus they are *exo*.³⁾

The detail of stereochemistry, the optical resolution of racemate and the antiarrhythmic activity of optical isomers of (**1**: Ar=C₆H₅, R=CH₃, *n*=3) will be reported in the full paper.

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3) J. Briggs, F.A. Hart, and G.P. Moss, *Chem. Commun.*, 1970, 1506.