This method was successfully applied to the assay of glycine in uric acid hydrolyzates[1] and in plasma samples,[4] threonine in casamino acid[1] 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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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=C_6H_5, R=CH_3, n=3) hydrochloride.

5-endo-Hydroxybicyclo[2.2.1]heptane-2,3-di-endo-carboxylic acid γ-lactone[1] (**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 $^{\mathrm{KBr}}_{\mathrm{max}}$ cm^{-1}: 1770 (γ-lactone), 1690 (COOH). NMR ($CDCl_3$) δ: 1.33 (d,d C^3H, $J_{2,3}=5.0$ Hz, $J_{3,4}=2.0$ Hz); 1.49 (d,t C^2H, $J_{2,3}=5.0$ Hz, $J_{1,2}=1.5$ Hz, $J_{2,6\mathrm{exo}}=2.0$ Hz). The coupling constants for C^2H and C^3H indicated that they are exo.

2 was treated with acetyl chloride or phosphorous trichloride and then heated with alkylenediamine [$NH_2(CH_2)_nNR_2$] 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=CH_3, n=3): Colorless plates, mp 154°. *Anal.* Calcd. for $C_{14}H_{22}O_3N_2 \cdot 1/3H_2O$: C, 61.76; H, 8.45; N, 10.29. Found: C, 61.93; H, 8.26; N, 10.40.

(**1**: Ar=C_6H_5, R=CH_3, n=3)·HCl: Colorless plates (hygroscopic), mp 239°. *Anal.* Calcd. for $C_{21}H_{26}O_4N_2 \cdot HCl \cdot 1/3H_2O$: 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 $CDCl_3$) δ: 8.0—7.3 (5H, C_6H_5), 5.17 (1H, C^5H, broad d,t $J_{5,6\mathrm{endo}}=J_{4,5}=4.5$ Hz, $J_{5,6\mathrm{exo}}=10.5$ Hz), 3.6—3.1 (5H, includes C^2H, C^3H, C^4H, and $CO)_2NCH_2$), 2.6—1.9 (9H, includes C^7H_2, C^6H_{endo}, and the remaining side chain CH_2). The coupling constants for C^5H indicated, from Jackman and Sternhell,[2] that C^5H is exo.

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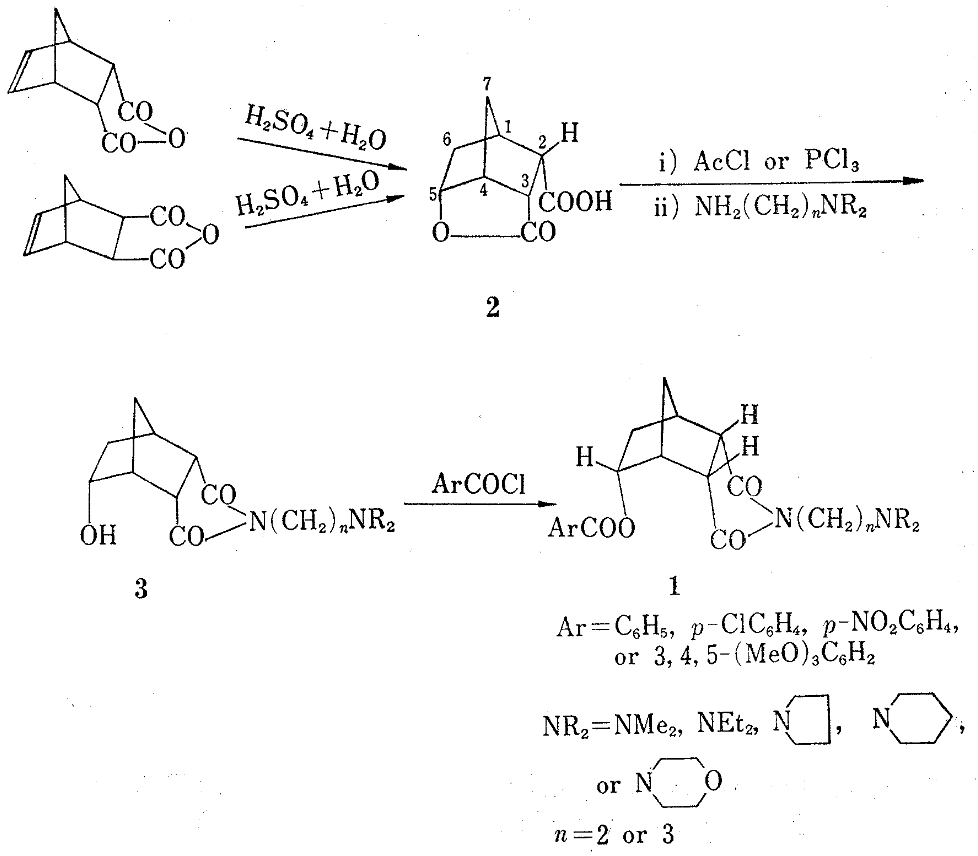

Ar=C_6H_5, p-ClC_6H_4, p-$NO_2C_6H_4$, or 3, 4, 5-$(MeO)_3C_6H_2$

NR_2=NMe_2, NEt_2,

n=2 or 3

Chart 1

The use of $Eu(fod)_3$ in the $CDCl_3$ spectrum provided adequate separation for the C^2H and C^3H signal. Both the C^2H and C^3H 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=C_6H_5, R=CH_3, n=3) will be reported in the full paper.

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