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A SYNTHESIS OF 2-AMINONORBORNENE-2-CARBOXYLIC ACID DERIVATIVES BY DIELS-ALDER REACTION USING α,β-DEHYDROALANINATES AS A DIENOPHILE

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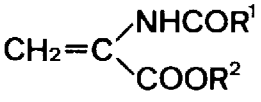
ABSTRACT The Diels-Alder reaction of N-acyl-α,β-dehydroalanine esters with cyclopentadiene afforded a mixture of the stereoisomers of acylaminonorbornene-2-carboxylic acid esters in good yields.

Several non-metabolizable analogs of natural amino acids are known to possess unique biological properties in that they affect amino acid transport.1) Of these amino acids, cycloaliphatic amino acids such as those having a norbornane skeleton are of interest because of their noticeable biological activities.2) These amino acids have been synthesized usually from the corresponding carbonyl compounds by Strecker or Bucherer synthesis. In conjunction with the biological interest of the cycloaliphatic amino acids, we have directed our attention to the development of a new methodology, based on the use of α,β-dehydroamino acids, for a synthesis of these amino acids.

The potential value of the N-acyl-α,β-dehydroamino acid esters in synthetic chemistry is derived in large part from their ready availability3)4) and their intrinsic reactivity5) of the double bonds due to the presence both of acylamino and ester groups which facilitate the attack of nucleophilic addends at the α and β positions. This communication reports a new approach to a synthesis of bicycloaliphatic amino acids, 2-aminonorbornene-2-carboxylic acid derivatives, by Diels-Alder reaction using N-acyl-α,β-dehydroalaninates (1) as a dienophile.



$$CH_2{=}C\begin{matrix} \diagup NHCOR^1 \\ \diagdown COOR^2 \end{matrix}$$

1

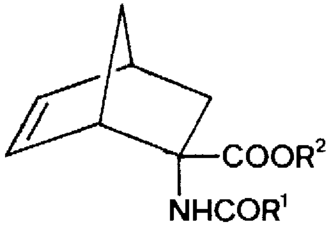
a, R^1=CH_3 ; R^2=CH_3

b, R^1=CH_3 ; R^2=CH_2CH_3

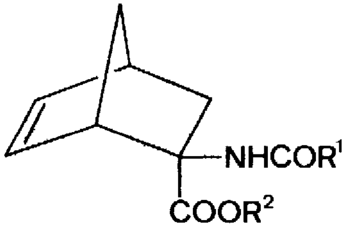
c, R^1=CH_3 ; R^2=CH_2Ph

d, R^1=OCH_3 ; R^2=CH_3

Methyl N-acetyl-α,β-dehydroalaninate (1a) was allowed to react with 3 molar equivalents of cyclopentadiene in toluene at 90-110°C for 5 hr to afford the cycloadducts (2a) in 77% yield. The adducts were readily separated into the *exo* isomer (mp 148-149°C) and the *endo* isomer (mp 132-133°C) by means of column chromatography on silica gel. The ratio of the *exo* isomer to the *endo* one is 5.7: 4.3. The structural assignments were made on the basis of the relative positions of the NMR signals of the protons on the substituents at C-2: the shielding effect[6)] of the double bond of 2-substituted 5-norbornene derivative leads the signals of the protons of the *endo* substituents to a higher field than those of the *exo* substituents. For example, the NMR spectra of the *exo* and *endo* adducts are as follows: $2a_{exo}$, δ ($CDCl_3$) 1.91 (s, 3H, $-NHCOC\underline{H}_3$), 3.75 (s, 3H, $-COOC\underline{H}_3$); $2a_{endo}$, δ ($CDCl_3$) 1.98 (s, 3H, $-NHCOC\underline{H}_3$), 3.63 (s, 3H, $-COOC\underline{H}_3$). The other N-acyl-α,β-dehydroalaninates (1b,c) were also treated with cyclopentadiene under the same conditions as above to afford the corresponding cycloadducts in 67-71% yields: the ratio of the *exo* isomer to the *endo* one in the adducts (2b) is 6.4: 3.6, while the ratio of the adducts (2c) is 6.7:3.3. It should be noted that in the Diels-Alder reaction of methyl N-methoxycarbonyl-α,β-dehydroalaninate (1d) with cyclopentadiene, no *endo* isomer could be detected but the *exo* isomer formed exclusively.[7)] In Table 1 are summarized the reaction conditions and the yields of the cycloadducts.



2 exo



2 endo

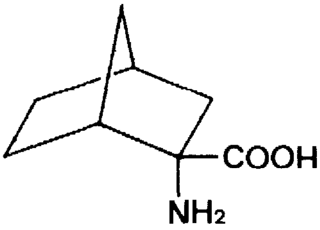
The cycloaddition reactions did not occur in an aprotic solvent such as ether or benzene at room temperature. The reaction was effected by heating the reaction mixture at 90°C.[8)] The addition of a Lewis acid such as $AlCl_3$ or $FeCl_3$ to the above reaction mixture accelerated the reaction, and forced it to proceed even at room temperature. However, the ratio of the stereoisomers in the Lewis acid-catalyzed reactions was almost the same as that without the catalyst,[9)] as shown in Table 1.

Table 1. Diels-Alder reactions of dehydroamino acids(1) with cyclopentadiene[a]

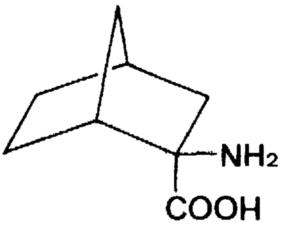
Substrate	Reaction temp.(°C)	Reaction time(hr)	Lewis acid	Yield of adduct(%)[b]	Adduct ratio[c] Exo : Endo
1a	90-110	5	-	77	5.7 : 4.3
1b	90-110	7	-	71	6.4 : 3.6
1b	25-30	7	$AlCl_3$[d]	79	6.3 : 3.7
1b	25-30	7	$FeCl_3$[e]	62	6.4 : 3.6
1c	90-110	6	-	67	6.7 : 3.3
1d	90-110	5	-	56	10.0 : 0

a) The reactions were carried out in toluene. b) Isolated yields. c) Determined by NMR analysis of crude products. d) Solvent,carbon-tetrachloride. e) Solvent,ether.

The cycloadducts, $2a_{exo}$ and $2a_{endo}$, thus obtained were converted into biologically active 2-aminonorbornane-2-carboxylic acids, 3_{exo} and 3_{endo},[10] respectively, via hydrogenation over Pd/C and subsequent hydrolysis with 6N-HCl.



3exo



3endo

The Diels-Alder reaction using the α,β-dehydroamino acids as a dienophile will give promise of synthetic application to a wide range of amino acids having interesting carbon-skeletons.

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References and Footnotes

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7) The reasons for the exclusive formation of the *exo* isomer are not obvious. We are extending our study with the systems of this type to help us gain a better understanding of the effect of the N-acyl groups on the stereochemistry of the cycloadducts. The lack of *endo* selectivity in the Diels-Alder reactions of 2-substituted acrylates with cyclopentadiene has been discussed by several authors. See, for example, Y. Kobuke, T. Fueno, and J. Furukawa, J. Am. Chem. Soc., 92, 6548 (1970).
8) It seems likely that the mesomeric effect of the N-acylamino group attached to acrylates does not so retard Diels-Alder reaction as that of alkoxy group. See, J. Quick and R. Jenkins, J. Org. Chem., 43, 2275 (1978).
9) The correlation between the *endo* selectivity and the reaction rate of the Diels-Alder reactions has recently been documented. See, K. Seguchi, A. Sera, Y. Otsuki, and K. Maruyama, Bull. Chem. Soc. Jpn., 48, 3641 (1975).
10) We thank Prof. H. N. Christensen who kindly sent us a copy of the NMR spectra of compound (3_{exo}) and compound (3_{endo}).

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