The Synthesis of Cyclic Amino Acids from Dialdehydes and Nitroacetates

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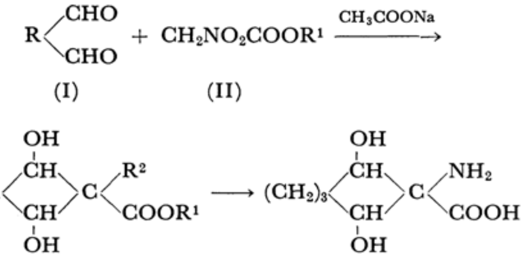
This is a report dealing with a new method for the synthesis of cyclic amino acids, shown as V of Chart 1.

The equimolecular reaction of dialdehydes (I) with nitroacetic esters[1] (II) in ethanol in the presence of sodium acetate at about 10°C gave the cyclic nitro-ester (III). Catalytic hydrogenation[*1] of IIIa with Raney nickel T-4[2] under 50 p.s.i.g. yielded the corresponding cyclic amino acid (V).

The following compounds were prepared by applying the above steps: starting from glutaraldehyde (25% aq. solution) and ethyl nitroacetate, 2-ethoxycarbonyl-2-nitrocyclohexane-1,3-diol (IIIa) (mp 95—97°C, recrystallized from benzene, 40% yield) was obtained; when benzyl nitroacetate[3] and *o*-phthalaldehyde were used in the reaction, the corresponding benzyloxycarbonyldiol (IIIb), mp 87—90°C, and indanediol (IIIc), (mp 111—112°C, from benzene, 71% yield) were obtained, respectively.

Hydrogenation of IIIa and IIIc gave 2-ethoxycarbonyl-2-aminocyclohexane-1, 3-diol (IVa), mp 149—150°C (ethyl acetate, 30% yield) and ethyl 2-amino-1, 3-dihydroxyindane-2-carboxylate (IVc), mp 161—162.5°C, respectively.

Hydrolysis of IVa using barium hydroxide gave the corresponding cyclic amino acid: 1-amino-2, 6-dihydroxycyclohexane-1-carboxylic acid (V), mp >300°C (water) in 89% yield.



(I) (II)

(III): $R^2=NO_2$
(IV): $R^2=NH_2$

(V)

	R	R^1		R	R^1
IIIa:	$-(CH_2)_3-$	Et	IVa:	$-(CH_2)_3-$	Et
IIIb:	$-(CH_2)_3-$	$-CH_2C_6H_5$	IVc:	o-C_6H_4	Et
IIIc:	o-C_6H_4	Et			

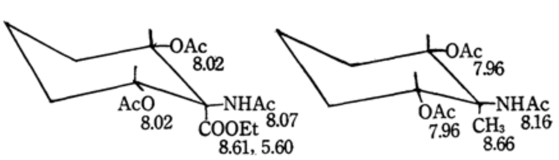
Chart 1

Acetylation of IVa yielded 2-acetamido-di-*O*-acetyl-2-ethoxycarbonylcyclohexane-1, 3-diol (VI), mp 109—110°C (isopropyl ether); its NMR spectrum in deuteriochloroform exhibited sharp signals at 8.07 τ for the equatorial acetamido group and at 8.02 τ for the two equatorial acetoxy groups and at 8.61, 5.60 τ for the ester group, respectively shown as Chart 2.

To confirm the above configuration, 2-acetamido-di-*O*-acetyl-2-methylcyclohexane-1, 3-diol (VII), mp 177.5—178°C (ethanol), was synthesized from 2-amino-2-methylcyclohexane-1, 3-diol, mp 215—217°C, which was obtained from 2-nitro-2-methylcyclohexane-1, 3-diol (VIII), mp 135—136°C (ethyl acetate - ligroin) by catalytic hydrogenation. VIII was prepared from nitroethane by a modification of the reaction known as "nitromethane-dialdehyde cyclization."[4]

The NMR spectrum of VII (in $CDCl_3$) showed three characteristic sharp signals which indicated the presence of two equatorial *O*-acetoxy groups (observed at τ, 7.96), an equatorial acetamido group (τ, 8.16) and an axial *C*-methyl group (τ, 8.66).

It has then been revealed that VI has its ethoxycarbonyl group at the axial C-1 position.



(VI) (VII)

Chart 2

The cyclization reaction using other nitroparaffins, nitroesters and dialdehydes obtained through periodate oxidation of sugars is in progress.

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1) S. Umezawa and S. Zen, This Bulletin, **36**, 1143 (1963).
2) S. Nishimura, *ibid.*, **32**, 61 (1959).
[*1] Hydrogenation Apparatus Paar Instruments.
3) A. Taylor (Imperial Chemical Industries Ltd.), Brit. Pat. 835521 (1960).
4) F. W. Lichthenthaler and H. O. Fischer, *J. Am. Chem. Soc.*, **83**, 2005 (1961); *Angew. Chem.*, **76**, 84 (1964).