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Note

Separation of N-carbomethoxy-1,2- and -1,4-dihydropyridines by thin-layer and column chromatography

JOHN R. McDONALD and CHARLES HOUGHTON
Department of Biological Sciences, Napier College, Edinburgh EH10 5DT (Great Britain)
and
A. JOHN SHAND*
Department of Chemistry, Napier College, Edinburgh EH10 5DT (Great Britain)
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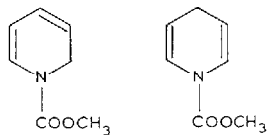
Simple dihydropyridines have been proposed as intermediates on the microbial metabolic pathways of various N-substituted pyridines[1–5]. In order to test this hypothesis in relation to the N-methylpyridinium ion, the synthesis of N-methyl-1,2- and -1,4-dihydropyridines was necessary. Difficulties have been experienced in the preparation of these simple dihydropyridines from pyridine due to lack of convenient methods for their synthesis and the ease with which the compounds undergo oxidation and addition reactions[6,7]. Both dihydropyridines have been reported by Fowler[7] from lithium aluminium hydride reduction of the corresponding N-carbomethoxydihydropyridines (I) and (II), formed by sodium borohydride reduction of pyridine in the presence of methyl chloroformate.



I II

Careful control of the reaction conditions gave almost exclusively the 1,2-isomer, but where mixtures were formed, the 1,4-isomer can be obtained by removal of the 1,2-isomer by Diels–Alder adduct formation with maleic anhydride.

However, in our hands, the treatment with maleic anhydride besides removing the 1,2-isomer also resulted in a marked reduction in the yield of the 1,4-isomer. Therefore, the development of a procedure capable of separating both isomers was highly desirable. Fowler[7] indicated that separation could be achieved on a small scale by thin-layer chromatography (TLC) or gas–liquid chromatography although no details were reported.

In this report we describe the successful preparative-scale separation of (I) and (II) by column chromatography on silica gel which then allows the formation of both the required N-methyldihydropyridines on further reduction.

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TABLE I

R_F VALUES OF N-CARBOMETHOXY-1,2- AND -1,4-DIHYDROPYRIDINE USING TLC

For solvent systems A–D, see text.

Compound	R_F			
	A	*B*	*C*	*D*
N-Carbomethoxy-1,2-dihydropyridine	0.93	0.06	0.05	0.97
N-Carbomethoxy-1,4-dihydropyridine	0.79	0.69	0.67	0.35

EXPERIMENTAL

Mixtures of N-carbomethoxy-1,2- and -1,4-dihydropyridines were prepared according to Fowler[7].

TLC was carried out on 0.2 mm Kieselgel 60 F_{254} plates (E. Merck, Darmstadt, G.F.R.) using the following solvent–solvent systems: (A) diethyl ether; (B) light petroleum (b.p. 60–80°)–ethyl acetate (9:1); (C) light petroleum (b.p. 60–80°)–diethyl ether (9:1); (D) chloroform.

Aliquots (10–20 μl) of the N-substituted dihydropyridine mixture (0.15–0.30 nmol) were applied to the plates. After developing, the plates were examined under ultraviolet light of wavelength 254 nm; the compounds gave dark spots against a yellow fluorescent background.

Column chromatography was performed using a 2 × 20 cm bed of silica gel L-528 (30–200 mesh) (May and Baker, Dagenham, Great Britain). The flow-rate of eluting solvent was 3–5 $cm^3 min^{-1}$ and the eluate was monitored continually at 265 nm.

RESULTS AND DISCUSSION

All four of the above solvent systems effectively separated (I) and (II) using TLC (Table I).

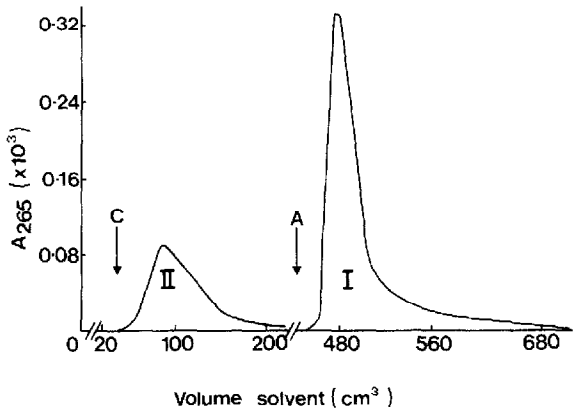

Fig. 1. Separation of N-carbomethoxydihydropyridines by column chromatography. A mixture of N-carbomethoxy-1,2- and -1,4-dihydropyridines (2 g) was applied to the top of the 20 × 2 cm silica gel L528 column (30–200 mesh). N-Carbomethoxy-1,4-dihydropyridine (II) was eluted using 400 cm^3 of solvent system (C). Thereafter, 300 cm^3 of solvent A was employed to elute the 1,2-isomer (I). The flow-rate was 3-5 $cm^3 min^{-1}$ and the eluate was collected in 10-cm^3 fractions, the absorbance of which was determined at 265 nm.

Subsequently, solvent systems C and A were selected for the separation of dihydropyridines by column chromatography on silica gel. Following the application of a mixture of the dihydropyridines to the column, N-carbomethoxy-1,4-dihydropyridine was eluted with solvent system C and thereafter, the 1,2-isomer with solvent A (Fig. 1). The separated isomers were characterised by their ultraviolet and infrared spectra which were in agreement with data previously obtained[7].

This method of separation of the dihydropyridines allows the preparation and purification of both isomers (I) and (II) in one synthetic step without loss of either isomer, prior to the formation of the respective N-methyldihydropyridines.

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