IMPROVED SYNTHESIS OF N-ALKYL-ASPARTIC ACIDS

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N-Alkyl-aspartic acids can now be prepared readily by nucleophilic addition of primary amines to the double bond of monomethyl maleate according to a technique first described by Zilkha and Bachi (1).

During the preparation of some N-alkyl-aspartic acids, we found that triethylamine could advantageously replace pyridine as solvent and catalyst. The yields are about 20% higher and the isolation of a much purer product is possible owing to the absence of colored secondary products.

We have extended this reaction to two more primary amines and we have obtained good yields of the following derivatives: N-ethyl-aspartic acid β-methyl ester (95%) and N-isopropyl-aspartic acid β-methyl ester (75%).

We also found that this method is quite general and that other types of amines can be used to give new N-alkyl-aspartic-acid β-methyl esters. Piperidine, ethanolamine, 2-propanolamine, and glycine methyl ester were condensed with monomethyl maleate to give the expected N-alkyl-aspartic acids β-methyl ester with yields of 76%, 75%, 82%, and 75% respectively.

When 2 equivalents of the amine were used, we obtained the corresponding N,N′-disubstituted asparagine: thus N,N′-dibutyl-asparagine and N,N′-dipiperidyl-asparagine were obtained.

Good yields of the N-alkyl-aspartic acids were obtained by hydrolysis of the corresponding methyl esters with cold barium hydroxide (1). All these amino acids were characterized as such except for N-(2-propanol)-aspartic acid, which is hygroscopic and was isolated as the copper salt.

EXPERIMENTAL

Preparation of N-Alkyl-aspartic Acids β-Methyl Esters

Maleic anhydride (56 g, 0.57 mole) was dissolved in 200 ml of methanol. After the mixture was refluxed on a water bath for 30 minutes, excess methanol was distilled off. One hundred milliliters of triethylamine was added to the residue, cooled in ice, very slowly and with stirring in order to avoid side reactions which could contaminate the product with colored by-products. One-half mole of the desired amine was then added in one portion. This mixture was stirred over a water bath for an hour. Usually the product started to crystallize in 20 minutes. The mixture was filtrated and washed twice with hot acetone or ethyl acetate. After these washings, the product is usually white and can be used without further purification (see Table I).

If necessary, the ester can be crystallized from a minimum volume of hot water by adding a large amount of acetone.

The addition of piperidine goes smoothly at room temperature and it is not necessary to heat the solution. However, in this reaction no solid crystallizes out, and the excess of triethylamine has to be evaporated, because the addition product remains in solution. The residue is taken in hot isopropanol and crystallized in the cold. A further crop of crystals is obtained after the addition of petroleum ether.

In the case of glycine methyl ester, 5 g (0.036 mole) of the hydrochloride were mixed with monomethyl maleate prepared from 5 g of maleic anhydride. To this mixture were added 30 ml of triethylamine and 5 ml of methanol. After heating on a water bath for an hour, the hydrochloride of triethylamine crystallized in the cold and was eliminated by filtration. The methanol and the excess of triethylamine were distilled off. The condensation product was dissolved in water and crystallized by the addition of isopropanol.

Preparation of N-Alkyl-aspartic Acids

The N-alkyl-aspartic acid methyl ester to be hydrolyzed (0.10 mole) was dissolved in 0.125 mole barium hydroxide solution and left for 2 hours at room temperature. The solution was heated for 10 minutes and

TABLE I

N-Alkyl-aspartic acids β-methyl esters

$CH_3—OOC—CH_2—\underset{\displaystyle NH\\ \displaystyle R}{\overset{\displaystyle |}{\underset{\displaystyle |}{CH}}}—COOH$

R	Yield (%)	M.p. (°C)	Formula	% nitrogen Calc.	% nitrogen Found
Ethyl	92	217	$C_7H_{13}NO_4$	7.99	7.93
Isopropyl	75	214	$C_8H_{15}NO_4$	7.39	7.35
Butyl*	80	231	$C_9H_{17}NO_4$	6.89	6.82
Cyclohexyl†	90	216	$C_{11}H_{19}NO_4$	6.11	6.16
Allyl‡	84	213	$C_8H_{13}NO_4$	7.48	7.43
Ethanol-2	75	198	$C_7H_{13}NO_5$	7.32	7.35
Propanol-2	82	200	$C_8H_{15}NO_5$	6.82	6.77
Piperidyl	76	164	$C_{10}H_{17}NO_4$	6.50	6.41
Methyl acetate	75	164	$C_8H_{13}NO_6$	6.39	6.57

*Reported (1) m.p. 220° C.
†Reported (1) m.p. 210° C.
‡Reported (1) m.p. 213° C.

then an equivalent of hot sulphuric acid (1.0 *M*) was added. The filtrated solution was evaporated to 30 ml. The amino acid was usually obtained by the slow addition of 200 to 500 ml of an organic solvent (see Table II).

TABLE II

Preparation of N-alkyl-aspartic acids

$HOOC—CH_2—\underset{\displaystyle NH\\ \displaystyle R}{\overset{\displaystyle |}{\underset{\displaystyle |}{CH}}}—COOH$

R	Yield (%)	M.p. (°C)	Formula	Solvent used for crystallization	% nitrogen Calc.	% nitrogen Found
Ethyl	95	190	$C_6H_{11}NO_4$	Ethanol	8.68	8.66
Isopropyl	98	185	$C_7H_{13}NO_4$	Ethanol	7.99	7.92
Ethanol-2	90	182	$C_6H_{11}NO_5$	Isopropanol	7.90	7.85
Propanol-2*	95	—	—	—	5.53	5.37
Piperidyl	75	185	$C_9H_{15}NO_4$	Acetone and ether	6.95	6.81
Carboxymethyl†	95	191	$C_6H_9NO_6$	Isopropanol	7.32	7.22

*Hygroscopic, characterized as copper salt.
†Reported (2) m.p. 198–199°.

N,N'-Dipiperidyl-asparagine

Fifty-one grams (0.60 mole) of piperidine (without triethylamine) were added to 38.2 g (0.29 mole) of monomethyl maleate prepared as described previously from 29 g of maleic anhydride. The mixture was heated over a water bath for 6 hours, then dissolved into 150 ml of isopropanol. N,N'-Dipiperidyl-asparagine crystallized slowly in the cold giving 30 g of white solid, which can be crystallized from ethanol by adding petroleum ether. Yield 56%; m.p. 192°. Calc. for $C_{14}H_{24}N_2O_3$: N, 10.43%. Found: N, 10.52%.

N,N'-Dibutyl-asparagine

To the methyl maleate obtained from maleic anhydride (21 g, 0.21 mole) and methanol were added 40 g (0.55 mole) of anhydrous butylamine and 50 ml of triethylamine. The mixture was heated on a water bath with stirring for 3 hours. The solid formed was filtered and washed twice with acetone. The melting point after recrystallization from water was 242°. Yield 70%. Calc. for $C_{12}H_{24}N_2O_3$: N, 11.46%. Found: N, 11.52%.

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THE SYNTHESIS OF SOME BASIC DIPHENYL ETHERS

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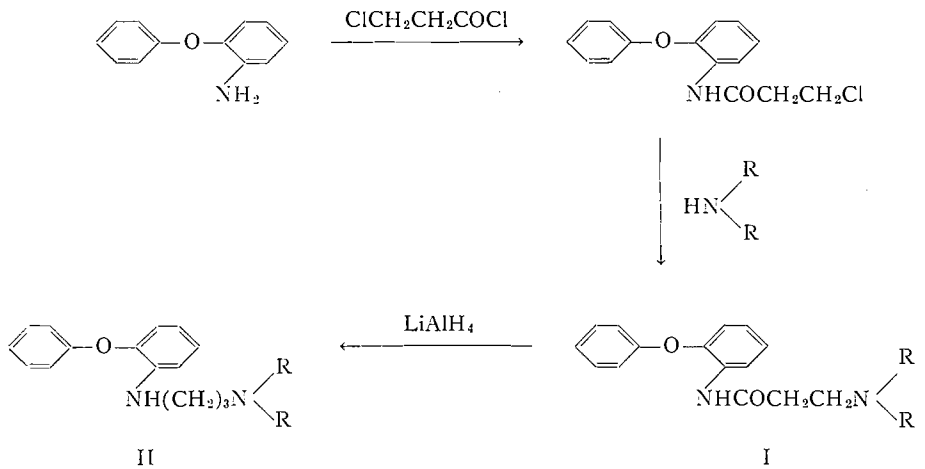
Recently several publications and patents (1–4) have appeared which described the synthesis and physiological activity (4) of 10-dialkylaminoalkylphenoxazines. In this communication we wish to describe the synthesis of some basic aromatic ethers, including two series of compounds, 2-(3-dialkylaminopropionamido)diphenyl ethers (I) (see Table I) and 2-(3-dialkylaminopropyl)diphenyl ethers (II) (see Table II), which may be regarded as open-chain analogues of the corresponding phenoxazine derivatives.

The basic ethers I and II were prepared from 2-aminodiphenyl ether according to the reaction scheme shown below.



In order to study further the relationship of structure to physiological activity in this series, some 4-(3-dialkylaminopropionamido)-2-nitrodiphenyl ethers (III) (see Table III) were synthesized in the same way as I, starting from 4-amino-2-nitrodiphenyl ether.