PRELIMINARY COMMUNICATION

A Simple Synthesis of Some Analogues of Natural Antibiotics

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The development of the simple and efficient methods of synthesis of unnatural analogues of natural compounds from readily available starting materials has become an important problem in our research group in the last years. Probably, one of the best possibilities for utilization of this effort offers 7-*exo*-oxohimic anhydride (*I*). Recently, this cheap and readily available *exo*-Diels—Alder adduct of furan and maleic anhydride [1] was used by us as a vehicle, which in turn reacted with chlorides of ammonia acids *II* in the presence of Et_3N with the release of furan to give requisite novel chiral imides *III* (Scheme 1) in good to moderate yields [2].

As a further product in all cases chiral *N*-substituted fumaramide *IV* was formed (20—60 %). Since the formation of chiral fumaric acid derivatives *IV* is very rare we have focused our interest to finding out some new methods for the synthesis of fumarates *IV* possessing potential biological activity.

It is known that fumaric acid and its derivatives belong to compounds having biological activity [3]. Fumaric acid occurs in many plants – for instance *Fumaria officinalis*, *Boletus scaber*, or it is produced by *Rhizopus nigricans*. It is essential to vegetable and animal tissue respiration. The compounds related to amides *IV* are very rare, for example (*E*)-*N*-(phenylacetyl)butenediamide *V* (*Fumaramidmycin*), isolated from *Streptomyces kurssanovii*, active against gram-positive and -negative bacteria was prepared enzymatically from *Streptomyces ishigakiensis* [4*a*—*d*]. *N*-(1-Carboxyethyl)-N^3-fumaramoyl-2,3-diaminopropanamide *VI*, the metabolite of *Streptomyces collinus* with a broad antibiotic activity [5], was prepared by *van der Baan* [6].

Birkinshaw and coworkers [7] isolated in 1942 a new metabolite of *Aspergillus niger*, which showed antibacterial activity. The structure of this metabolite was confirmed by *Birch* [8] in 1968 as (*S*)-*N*-(1-carboxyethyl)fumaramic acid (*VII*). The first synthesis of racemic (±)-*VII* was published 10 years later by *Rossi* [9], (±)-*VII* was prepared from fumaric acid chloride monomethyl ester and alanine in the presence of $NaHCO_3$ in water at 0 °C, in 52 % yield.

Despite these important biological properties, there are only a few reports in the literature on the synthesis of analogues of active fumaric acid derivatives. Most methods involve reactions of fumaric acid chloride or ester, or enzymatic route is developed. This communication reports on a new method of the synthesis of *IV*, namely (*S,E*)-*N*-{1-[1,2-bis(ethoxycarbonyl)]ethyl}fumaramic acid diethyl (*IVa*).

As has been mentioned, the use of Et_3N as a base in the reaction of amino acid derivatives *IIa*, *IIb* with *I* (Scheme 1) leads to the formation of two products *III* and *IV* [2], therefore we had to try some other bases. *Junek* and coworkers observed the isomerization of *N*-carbamoylmaleamic acid to *N*-carbamoylfumaric acid under the heating of reaction mixture to 70 °C in the presence of pyridine for 10 min in 86 % yield [10].

On the basis of this report we have stirred diethyl (*S*)-aspartate chloride *II* with *I* in the presence of pyridine in refluxing toluene for 17 h. In contrast to triethylamine in the case of pyridine as a base only the signals for the expected form *IVa* were detected in the ^1H NMR spectra in the crude original reaction mixture. The yellow crude reaction mixture was evaporated to dryness, dissolved in CH_2Cl_2 and evaporated with silica gel to dryness and column chromatography (eluent i-hexane—ethyl acetate, φ_r = 4 1, 40 g of silica gel of the grain size 40—60 μm, 35 cm × 1.5 cm) gave the required product (*S,E*)-*N*-{1-[1,2-

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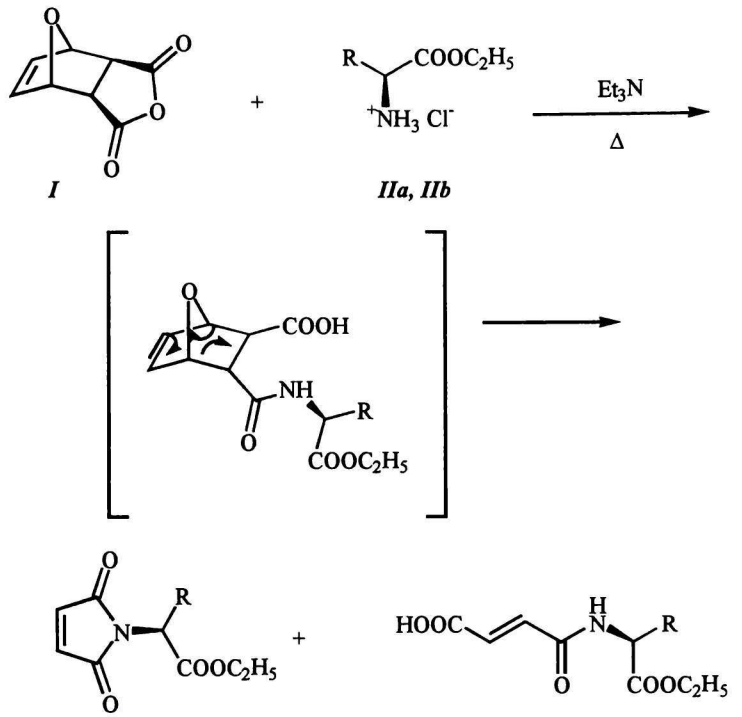
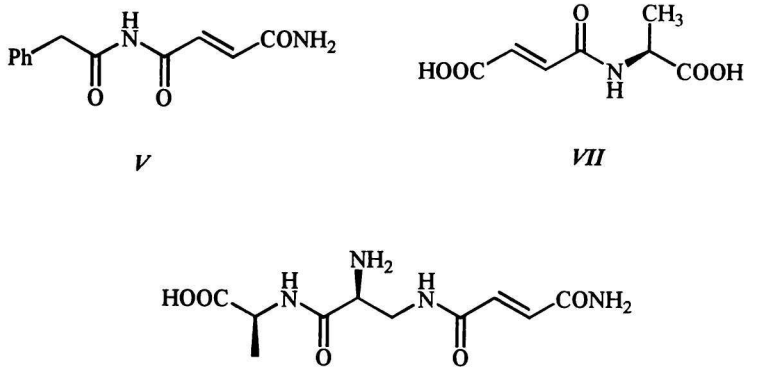


I *IIa, IIb* *IIIa, IIIb* *IVa, IVb*

a R = $CH_2COOCH_2CH_3$

b R = $CH(CH_3)_2$

Scheme 1



V *VII* *VI*

Scheme 2

bis(ethoxycarbonyl)]ethyl}fumaramic acid (*IVa*) in 50 % yield, m.p. = 137—140°C. For $C_{12}H_{17}NO_7$ (M_r = 287.27) w_i(calc.): 50.17 % C, 5.96 % H, 4.88 % N; w_i(found): 50.13 % C, 6.06 % H, 4.72 % N. ^{1}H NMR spectrum ($CDCl_3$—CD_3OD), δ: 1.27 (6H, 2 × t, $OCH_2\underline{CH_3}$), 2.88 (1H, dd, J = 17.0 Hz, 4.9 Hz, CH_2), 3.02 (1H, dd, CH_2), 4.16 (2H, q, $O\underline{CH_2}CH_3$), 4.24 (2H, q, $O\underline{CH_2}CH_3$), 4.90 (1H, m, N—CH), 6.79 (1H, d, J = 16.6 Hz, =CH), 7.00 (1H, d, =CH). ^{13}C NMR spectrum ($CDCl_3$—CD_3OD), δ: 13.82 (q, $OCH_2\underline{CH_3}$), 36.04 (d, CH), 48.81 (t, CH_2), 61.13 (t, $O\underline{CH_2}CH_3$), 61.97 (t, $O\underline{CH_2}CH_3$), 131.19 (d, =CH), 135.71 (d, =CH), 163.85, 167.80, 170.26, 170.82 (s, C=O).

The similar product was obtained in the case of valine derivatives *IVb*. ^{1}H NMR spectrum ($CDCl_3$), δ: 0.91 (3H, d, $J = 19.1$ Hz, CH_3), 1.00 (3H, d, CH_3), 1.25 (3H, t, $OCH_2\underline{CH_3}$), 2.30 (1H, m, CH), 4.20 (2H, q, $O\underline{CH_2}CH_3$), 4.65 (1H, dd, $J = 4.7$ Hz, CH—NH), 6.80 (1H, d, $J = 15.4$ Hz, =CH), 7.10 (1H, d, =CH).

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