Transformations Starting from Biotechnologically Available Materials
III.* *N*-Arylcitraconimides Resulting from Addition of Amines to *N*-Arylitaconimides

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Transformation of *N*-arylitaconimides into methyl *N*-arylsuccinimides or *N*-arylcitraconimides is described. The resulting 3-substituted methyl *N*-arylsuccinimides revealed fungicidal and anti-yeast activities.

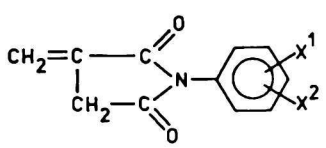
Pesticidal properties of 2-methylenebutanedioic (itaconic) acid were reported already in the fortieth [1]. Our preceding papers [2, 3] described the preparation of itaconic acid esters, amides and imides, of which especially imides showed interesting effects against phytopathogenic moulds.

This paper presents derivatization of the methylene group of some selected itaconimides with a perspective amino grouping in order to influence the biological activity of products obtained. This project was stimulated by the results with derivatization reported in various patents [4, 5]. Some papers [6—10] also stressed that nucleophilic additions to the exocyclic double bond gave rise to isomeric products.

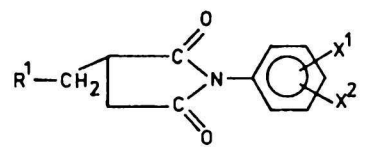
The starting *N*-arylitaconimides *Ia*—*Ie* are easily available from itaconic acid produced biotechnologically *via* the corresponding anhydride. The required addition products *IIa*—*IIe* were obtained on reaction with aziridine either in ether or in chloroform (derivative *Ie*) at room temperature. The reaction of imide *Ib* with *cis*-2,6-dimethylmorpholine proceeded analogously to give *N*-arylsuccinimide *IIf* in high yield. On the other hand, treatment with 4-chloroaniline failed, the desired addition product *IIg* could not be detected by thin-layer chromatography, although the reaction time was extended and the temperature was raised.

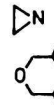
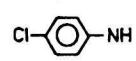
The exomethylene group of *N*-arylitaconimides *Ic* and *Ie* was functionalized also with primary and secondary amines (*tert*-butylamine, diisopropylamine, allylamine). Because analysis of the isolated products showed the empirical formulas to be $C_{11}H_8ClNO_2$ and $C_{11}H_7ClFNO_2$, respectively, it was concluded that neither addition nor elimination took place.

The ^1H NMR spectra of compounds *I* lacked signals of the alkyl moiety of the respective amine or the methylene group of *Ic* and *Ie*; on the other



	X^1	X^2
Ia	H	H
Ib	3-CF_3	H
Ic	3-Cl	4-F
Id	3-Cl	5-Cl
Ie	4-Cl	H



	R^1	X^1	X^2
IIa		H	H
IIb		3-CF_3	H
IIc		3-Cl	4-F
IId		3-Cl	5-Cl
IIe		4-Cl	H
IIf		3-CF_3	H
IIg		3-CF_3	H
IIh	$(C_2H_5)_2N$	3-CF_3	H

*For Part *I* see *Justus Liebigs Ann. Chem. 1990*, 111.

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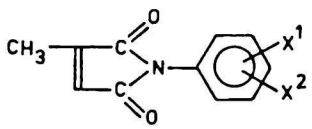
hand, doublets at δ = 2.17 and 6.48 appeared. The ^{13}C NMR spectrum displayed signals of an sp^2-quaternary carbon in lower field at δ = 145.96 and 146.05, respectively and singlets of an sp^3 carbon at δ = 11.19 and 11.21, respectively; these values are in accordance with those of *N*-arylcitraconimides [10, 11]. As reported [12], a considerably preferred equilibrium in favour of dimethyl mesaconate in comparison with dimethyl citraconate was observed on a base-catalyzed isomerization of dimethyl itaconate. The easiness of formation of citraconic derivatives in our experiments is associated with an existence of planary stabilized carbanions of a pyrrolidine-2,5-dione system. An addition product *IIb* was isolated from the reaction of the imide *Ib* with diethylamine in ether at – 10 °C (monitored by thin-layer chromatography) by a careful work-up of the mixture. Compound *IIb* in $CDCl_3$ freed spontaneously dimethylamine during a 12 h standing in the spectrometric probe to yield the isomeric *N*-arylcitraconimide *IIIc*.

Compounds *IIa—IIf* showed a significant effect in antimicrobial tests [13] against yeasts with MIC in the interval of 7.81 x 10^{-6} to 2.5 x 10^{-4} mol dm^{-3}; MIC of potassium sorbate used as standard was found to be 1 x 10^{-3} to 2 x 10^{-3} mol dm^{-3} The antibacterial and antifungal effects were lower than those of the standards.

EXPERIMENTAL

The melting points corrected, the ^1H and ^{13}C NMR spectra of deuterochloroform solutions containing tetramethylsilane as an internal reference were measured with an apparatus JX-100 (Jeol), the IR spectra of KBr pellets were recorded with a spectrophotometer PU 980.0 FTIR (Philips Analytical) and the mass spectra were run with an instrument MS 902 S (AEI, Manchester) at 70 eV ionizing electron energy. Solvents were distilled under reduced pressure (2—2.5 kPa) at 25—30 °C. Samples for analyses were dried over P_2O_5



	X^1	X^2
IIIa	4—Cl	H
IIIb	3—Cl	4—F
IIIc	3—CF_3	H

at 60 Pa and ambient temperature, other products in air at room temperature. The reaction course was monitored by thin-layer chromatography on Silufol (Kavalier) sheets and the spots were visualized by UV_{254} light or by iodine vapours. Silica gel (60—120 μm) was used for column chromatography in a compound to carrier mass ratio 1 : 30, elution with benzene. The products were crystallized from benzene—cyclohexane.

For antimicrobial tests following selected models of gram-positive (*Bacillus subtilis*, *Sarcina subflava*, *Staphylococcus aureus*, and *Micrococcus luteus*) and gram-negative (*Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, and *Salmonella typhimurium*) bacteria were employed. The effect against yeasts was tested with *Zygosaccharomyces baillii*, *Saccharomyces oviformis* Bratislava 1, *Pichia fermentants*, *Candida albicans*, *Saccharomyces cerevisiae* Hliník 1, *Kloeckera apiculata*, *Torulopsis bovina*, *Kluyveromyces marxianus*. The antifungal activity was tested with phytopathogenic fibrous fungi *Botrytis cinerea* and *Fusarium nivale*.

Substituted Methylpyrrolidine-2,5-diones *IIa—IIf*

Aziridine or *cis*-2,6-dimethylmorpholine (10 mmol) in ether (10 cm^3) was added to a stirred solution of *N*-arylitaconimide *Ia—Id* (10 mmol) in ether (30 cm^3), compound *Ie* in chloroform (80 cm^3), at 0 to 5 °C. The solvent was distilled off after a 24 h stirring at room temperature under diminished pressure and the residue was crystallized from benzene—cyclohexane (φ_r = 1 : 2), or eventually purified chromatographically.

1-Phenyl-3-(aziridin-1-yl)methylpyrrolidine-2,5-dione (IIa), yield 65 %, m.p. = 178—180 °C. For $C_{13}H_{14}N_2O_2$ (M_r = 230.3) w_i(calc.): 67.8 % C, 6.12 % H, 12.17 % N; w_i(found): 68.1 % C, 5.77 % H, 12.11 % N. IR spectrum, $\tilde{\nu}/cm^{-1}$: 1700, 1675, 3320. ^1H NMR spectrum, δ: 1.27, 1.73 (m, 4H, 2 x CH_2 aziridine), 2.65, 2.75 (2 x dd, 2H, CH_2), 3.15 (m, 3H, CH, CH_2), 7.3—7.46 (m, 5H, H_{arom}). Mass spectrum, *m/z*: 230 (M^+). ^{13}C NMR spectrum, δ: 26.63, 28.25 (t, t, 2 x CH_2 aziridine), 33.0 (t, CH_2), 41.16 (t, CH), 60.55 (t, N—CH_2), 128.59, 128.75, 129.13 (3 x dd, CH_{arom}, C-2′, C-4′, C-3′), 132.03 (s, C_{arom}, C-1′), 175.88 (s, C=O), 178.00 (s, C=O).

1-(3-Trifluoromethylphenyl)-3-(aziridin-1-yl)-methylpyrrolidine-2,5-dione (IIb), yield 73 %, m.p. = 100—101 °C. For $C_{14}H_{13}F_3N_2O_2$ (M_r = 298.3) w_i(calc.): 56.37 % C, 4.39 % H, 9.39 % N; w_i(found): 57.03 % C, 4.43 % H, 9.54 % N. IR spectrum, $\tilde{\nu}/cm^{-1}$: 3450, 1725, 1450. ^1H NMR spectrum, δ: 1.29, 1.76 (m, 4H, 2 x CH_2 aziridine),

2.69, 2.77 (2 x dd, 2H, CH_2), 3.14 (m, 3H, CH_2, CH). ^{13}C NMR spectrum, δ: 26.85, 28.35 (2 x t, 2 x CH_2 aziridine), 33.04 (t, CH_2), 41.30 (d, CH), 60.57 (t, N—CH_2), 123.40, 123.45, 123.51, 125.71, 129.72, 131.48, 132.57 (2 x d, 3 x q, 1 x s, C_{arom}, CF_3), 175.34 (s, C=O), 177.58 (s, C=O). Mass spectrum, *m/z*: 298 ($M^{+\bullet}$).

1-(3-Chloro-4-fluorophenyl)-3-(aziridin-1-yl)methylpyrrolidine-2,5-dione (IIc), yield 72 %, solidifying oil. For $C_{13}H_{12}ClFN_2O_2$ (M_r = 282.7) w_i(calc.): 55.23 % C, 4.28 % H, 9.91 % N; w_i(found): 55.61 % C, 4.33 % H, 9.86 % N. IR spectrum, $\tilde{\nu}$/cm^{-1}: 3350, 1710, 1625. ^1H NMR spectrum, δ: 1.26, 1.72 (m, 4H, 2 x CH_2 aziridine), 2.65, 2.75 (2 x dd, 2H, CH_2), 3.11 (m, 3H, CH, CH_2), 7.22, 7.42 (m, 3H, H_{arom}). ^{13}C NMR spectrum, δ: 26.84, 28.26 (2 x t, 2 x CH_2 aziridine), 32.94 (t, CH_2), 41.22 (d, CH), 60.49 (t, N—CH_2), 116.80, 117.10, 126.34, 126.47, 128.82 (5 x d, CH_{arom}, C-5′, C-6′, C-2′), 121.48, 121.75, 128.43, 128.50, 156.01, 159.34 (6 x s, C_{arom}, C-3′, C-1′, C-4′), 175.36 (s, C=O), 177.57 (s, C=O).

1-(3,5-Dichlorophenyl)-3-(aziridin-1-yl)methylpyrrolidine-2,5-dione (IId), yield 72 %, m.p. = 126—129 °C. For $C_{13}H_{12}Cl_2N_2O_2$ (M_r = 311.2) w_i(calc.): 50.18 % C, 3.89 % H, 9.00 % N; w_i(found): 50.40 % C, 3.72 % H, 8.81 % N. IR spectrum, $\tilde{\nu}$/cm^{-1}: 3500, 1720, 1475. ^1H NMR spectrum, δ: 1.28, 1.75 (m, 4H, 2 x CH_2 aziridine), 2.80 (m, 2H, CH_2), 3.17 (m, 3H, CH_2, CH), 7.25—7.48 (m, 3H, H_{arom}).

1-(4-Chlorophenyl)-3-(aziridin-1-yl)methylpyrrolidine-2,5-dione (IIe), yield 33 %, m.p. = 94—96 °C. For $C_{13}H_{13}ClN_2O_2$ (M_r = 264.7) w_i(calc.): 58.98 % C, 4.95 % H, 10.59 % N; w_i(found): 58.88 % C, 5.02 % H, 10.47 % N. IR spectrum, $\tilde{\nu}$/cm^{-1}: 1707, 1491, 1387. ^1H NMR spectrum, δ: 1.25, 1.72 (m, 4H, 2 x CH_2 aziridine), 2.62, 2.74 (2 x dd, 2H, CH_2), 3.10 (m, 3H, CH_2, CH), 7.25 (d, 2H, H_{arom}), J = 8 Hz, 7.45 (d, 2H, H_{arom}), J = 8 Hz. ^{13}C NMR spectrum, δ: 25.74, 27.23 (2 x t, CH_2 aziridine), 31.96 (t, CH_2), 40.15 (d, CH), 59.44 (t, N—CH_2), 126.65, 128.29 (2 x d, CH_{arom}), 129.49, 133.21 (2 x s, CH_{arom}), 174.53 (s, C=O), 176.69 (s, C=O). Mass spectrum, *m/z*: 265 ($M^{+\bullet}$).

1-(3-Trifluoromethylphenyl)-3-(cis-2,6-dimethylmorpholin-1-yl)methylpyrrolidine-2,5-dione (IIf), yield 78 %, m.p. = 74—76 °C. For $C_{18}H_{21}F_3N_2O_3$ (M_r = 370.4) w_i(calc.): 50.37 % C, 5.72 % H, 7.57 % N; w_i(found): 58.44 % C, 5.63 % H, 7.61 % N. IR spectrum, $\tilde{\nu}$/cm^{-1}: 1705, 1495. ^1H NMR spectrum, δ: 1.05, 1.10 (2 x d, 6H, 2 x CH_3), 1.94, 2.64 (m, 4H, CH_2 morpholine), 2.78, 2.83 (2 x dd, 2H, CH_2—N), J = 7.7 Hz, J = 2.7 Hz, 2.93, 2.97 (2 x dd, 2H, CH_2), J = 1 Hz, J = 1.6 Hz, 7.48—7.71 (m, 4H, H_{arom}). ^{13}C NMR spectrum, δ: 18.95, 19.06 (2 x q, 2 x CH_3), 33.36 (t, CH_2), 39.32 (d, CH pyrrolidine-2,5-dione), 58.4 (t, CH_2—N), 59.28, 60.58 (2 x t, CH_2 morpholine), 77.66, 74.71 (d, CH morpholine), 123.51 (q, CF_3), J = 270 Hz, 123.35 (q, CH_{arom}, C-2′), J = 44 Hz, 125.77 (q, CH_{arom}, C-4′), J = 3.7 Hz, 129.59 (d, CH_{arom}, C-5′), 129.73 (d, CH_{arom}, C-6′), 131.45 (q, CH_{arom}, C-3′), J = 34 Hz, 132.48 (s, CH_{arom}, C-1′), 175.23 (s, C=O), 177.64 (s, C=O). Mass spectrum, *m/z*: 370 ($M^{+\bullet}$).

1-(3-Trifluoromethylphenyl)-3-(diethylamino)-methylpyrrolidine-2,5-dione (*IIh*) and 1-(3-Trifluoromethylphenyl)-3-methyl-1*H*-pyrrole-2,5-dione (*IIIc*)

Three drops of pyridine and diethylamine (0.73 g; 10 mmol) in ether (5 cm^3) were added to a stirred solution of *N*-(3-trifluoromethylphenyl)itaconimide (2.5 g; 10 mmol) in ether (50 cm^3) at – 10 °C. The end of this reaction was indicated by disappearance of the starting imide *Ib* on thin-layer chromatography. The solvent was distilled off without heating and the oily residue *IIh* (2.6 g, 84 %) solidified on standing in a refrigerator. ^1H NMR spectrum, δ: 0.94 (t, 6H, 2 x CH_3), 2.50 (m, 2H, CH_2), 2.78 (q, 4H, CH_2), 2.86 (m, 3H, CH_2, CH), 7.51—7.63 (m, 4H, H_{arom}). This product underwent rearrangement into the substituted citraconimide *IIIc* on a 12 h standing as evidenced by the ^1H NMR spectrum, δ: 2.19 (d, 3H, CH_3), J = 1.8 Hz, 6.51 (q, 1H, CH), J = 1.8 Hz, 7.59—7.69 (m, 4H, H_{arom}). ^{13}C NMR spectrum, δ: 11.19 (q, CH_3), 122.49, 129.20, 127.69, 129.63 (4 x d, CH_{arom}, C-2′, C-4′, C-6′, C-5′), 131.35, 132.3, 128.8 (d, CH_{alkene}), 146.10 (s, C_{alkene}), 168.18 (s, C=O), 170.14 (s, C=O).

1-(4-Chlorophenyl)- (*IIIa*) and 1-(3-Chloro-4-fluorophenyl)citraconimide (*IIIb*)

One drop of pyridine was added into a solution of *Ie* (2.21 g; 10 mmol) resp. *Ic* in chloroform (30 cm^3). *tert*-Butylamine (1.2 g; 12 mmol) in ether (5 cm^3) was then introduced at 0 °C with stirring, which continued till all starting imide was consumed (thin-layer chromatography). The solvent was distilled off under reduced pressure and the product was crystallized from cyclohexane.

Yield *IIIa* 1.8 g (85 %), m.p. = 103—105 °C (Ref. [8] gives m.p. = 117 °C). For $C_{11}H_8ClNO_2$ (M_r = 221.6) w_i(calc.): 59.61 % C, 3.64 % H, 6.33 % N; w_i(found): 59.13 % C, 3.61 % H, 6.04 % N. ^1H NMR spectrum, δ: 2.17 (d, 3H, CH_3), J = 1.8 Hz, 6.48 (q, 1H, CH), J = 1.8 Hz, 7.31 (d, 2H, H_{arom}), J = 8.0 Hz. ^{13}C NMR spectrum, δ: 11.19 (q, CH_3), 126.94, 127.56, 129.44 (3 x d, C_{arom}), 130.19, 133.31 (2 x s, C_{arom}), 128.33 (d, C_{alkene}), 195.96 (s, C_{alkene}), 169.21, 170.30 (s, C=O). Mass spectrum, *m/z*: 221 ($M^{+\bullet}$).

Yield *IIIb* 88 %, m.p. = 104—105 °C. For $C_{11}H_7ClFNO_2$ (M_r = 239.6) w_i(calc.): 55.13 % C, 3.20 % H, 5.98 % N; w_i(found): 55.70 % C, 3.20 % H, 5.98 % N; IR spectrum, $\tilde{\nu}/cm^{-1}$: 1710, 1495. ^1H NMR spectrum, δ: 2.17 (d, 3H, CH_3), J = 1.8 Hz, 6.48 (q, 1H, CH), J = 1.8 Hz, 7.22—7.48 (m, 3H, H_{arom}). ^{13}C NMR spectrum, δ: 11.21 (q, CH_3), 116.89, 116.99, 125.54, 125.64, 127.56 (5 x d, CH_{arom}), 121.35, 121.60, 128.52, 128.77, 155.45, 158.76 (6 x d, CH_{arom}), 121.35, 121.60, 128.52, 128.77, 155.45, 158.76 (6 x s, C_{arom}), 146.05 (s, C_{alkene}), 168.97 (s, C=O), 170.11 (s, C=O), 128.02 (d, CH_{alkene}). Mass spectrum, *m/z*: 239 ($M^{+\cdot}$).

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