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Synthesis and Biological Activities of the Antibiotic B 371 and its Analogs

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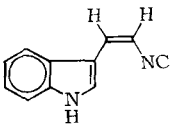
The synthesis of the title compound **1** is described as well as the syntheses of a series of structural analogs of type **4**. The antimicrobial *in vitro* activity of these vinyl isocyanides, substituted in β-position either by an indole derivative or by an aryl or 2-thienyl group, was tested against *Escherichia coli, Bacillus subtilis,* and *Mucor muhei* TÜ 284 (Table 1). Some of the compounds **4** display higher activity than the naturally occurring parent compound **1**. – A variety of alkyl 2-isocyanoacrylates of type **5** were included in the biological test. Some of them display exceptionally high antimicrobial activity (Table 2). Upon conversion of the isocyano group into the formamido group (**4** → **6**), the biological activity is lost.

Synthese und biologische Aktivität des Antibiotikums B 371 und seiner Strukturvarianten

Die Synthesen der Titelverbindung **1** und einer Reihe von Strukturvarianten des Typs **4** werden beschrieben. Die antimikrobiellen Aktivitäten dieser Vinylisocyanide, die in β-Position entweder ein Indolderivat oder eine Aryl- oder 2-Thienylgruppe tragen, wurden im Plattentest gegenüber *Escherichia coli, Bacillus subtilis* und *Mucor muhei* TÜ 284 geprüft (Tab. 1). Einige der Verbindungen **4** sind stärker wirksam als die natürlich vorkommende Stammverbindung **1**. – Eine Serie von Alkyl-2-isocyanacrylaten des Typs **5** wurde in den Test einbezogen. Einige davon sind außerordentlich stark aktiv (Tab. 2). Die Aktivität geht in allen Fällen verloren, wenn man die Isocyangruppe zur Formamidogruppe hydrolysiert (**4** → **6**).

The antibiotic B 371 produced by an unidentified species of *Pseudomonas* was suggested by *J. R. Evans* et al.[1] to have the structure **1**.



1

The *Z*-configuration was determined from the ^{1}H NMR spectrum by a coupling constant of 9 Hz for the vinylic protons. The strong IR absorption at 2138 cm^{-1} suggested an isocyanide structure but the isomeric nitrile was not excluded definitely.

Naturally-occurring isocyanides are relatively rare; of these the α,β-unsaturated compounds possess interesting antibacterial and/or antifungal activities[2].

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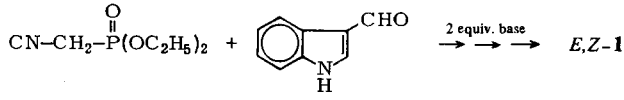
In this communication the synthesis of **1** and its analogs and their biological activities in disc diffusion tests are reported.

Synthesis

According to *Schöllkopf* et al.[3] α,β-unsaturated isocyanides are easily obtained from diethyl (isocyanomethyl)phosphonate **2** and carbonyl compounds.

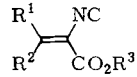


2 **3**

3-Indolecarbaldehyde (**3**) gave with **2** in the presence of two equivalents of base (*via* the anion of **3**) an *E/Z*-mixture of **1**. With lithium diisopropylamide as base the Wittig-Horner reaction led to *E*-**1** (63%) accompanied only by traces of *Z*-**1**. With sodium bis(trimethylsilyl)amide a 3:2-mixture of *E/Z*-**1** was obtained in 54% yield which was separated by chromatography on silica gel.

The spectroscopic data for *Z*-**1** are identical with those reported in lit.[1]. *E*- and *Z*-**1** are recognized in the ^{1}H NMR spectrum by their vinylic coupling constant of 14 and 9 Hz, respectively.

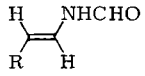
4



5

4	R
a	5-Bromo-3-indolyl
b	5-Methoxy-3-indolyl
c	2-Methyl-3-indolyl
d	5-Bromo-1-methyl-3-indolyl
e	1-Methyl-3-indolyl
f	5-Methoxy-1-methyl-3-indolyl
g	1,2-Dimethyl-3-indolyl
h	1-Ethyl-3-indolyl
i	1-Benzyl-3-indolyl
j	1-Diethoxyphosphoryl-3-indolyl
k	C_6H_5
l	4-$CH_3OC_6H_4$
m	2-Thienyl

5	R^1	R^2	R^3
a	C_6H_5	H	CH_3
b	C_6H_5	H	C_2H_5
c	3,4-$(CH_3O)_2C_6H_3$	H	CH_3
d	4-BrC_6H_4	H	*tert*-C_4H_9
e	2-Furyl	H	*tert*-C_4H_9
f	2-Thienyl	H	*tert*-C_4H_9
g	4-Pyridyl	H	*tert*-C_4H_9
h	3,4-$(CH_3O)_2C_6H_3$	CH_3	CH_3
i	CH_3	H	CH_3
j	CH_3	CH_3	CH_3
k	$(CH_3)_2N$	H	CH_3



6	R
a	3-Indolyl
b	1-Methyl-3-indolyl
c	C_6H_5

Analogously we prepared the vinyl isocyanides **4a – c** with a ring-substituted indolyl moiety and a free NH-group. Moreover, we synthesized the compounds **4d – j** with *N*-substituted indolyl groups as well as the β-aryl and the β-thienyl compounds **4k – m**.

Biological Activity

The vinyl isocyanides **1** and **4** were screened for antibacterial and antifungal activities against *Escherichia coli, Bacillus subtilis,* and *Mucor muhei* TÜ 284 by disc diffusion tests on agar plates incubated at 37 °C for 24 hours (for details see Experimental Part). The test results are summarized in Table 1. α-Isocyanoacrylates **5**, previously described by *Schöllkopf* et al.[4], were included in the study (cf. Table 2). Recently *Suzuki* et al.[5] became attentive of the biological activities of these type of compounds, too.

Toxicity: The acute LD_{50} (♀ mice, mg/kg) is 1470 for **5a** and >2150 for **5b**.

Results and Discussion

All of the β-indolylvinyl isocyanides (**1, 4a – j**) synthesized, exhibited antibacterial and strong antifungal activities. The *N*-alkylated derivatives **4e** and **h** showed higher fungicid activities than the *N*-unsubstituted compound. This may be explained by their greater chemical stability.

Striking is the increased antifungal activity caused by the thienyl substituent in the vinyl isocyanide **4m** as well as in the α-isocyanoacrylic ester series (cf. **5f**)[5].

Furthermore, the study shows that β-aryl (or heteroaryl) substitution is essential for the activity; the alkyl derivatives **5i** and **j** are virtually inactive. We also observed that β-disubstitution reduces the activity (cf. **5h** and lit.[5]). Since the formylamino compounds **6a – c** – the products of hydrolysis of the isocyano group – exhibit no antimicrobial activity (cf. Table 2), it is evident that the isocyanide group is essential for biological activity. In summarizing we conclude that vinyl isocyanides, β-(mono)substituted with an aromatic or heteroaromatic system, display considerable and even outstanding antimicrobial activity.

We are grateful to *BASF AG,* Ludwigshafen, for pharmacological and toxicological studies.

Experimental

Infrared spectra: Perkin-Elmer 157G. – ^{1}H NMR spectra: Varian HA 100. – UV spectra: Zeiss RPQ 20A spectrometer.

Thin-layer chromatography was carried out on precoated silica gel SIL G/UV_{254} (Macherey-Nagel & Co). Column chromatography was performed on Kieselgel 60, 230 – 400 mesh (Merck) with 1 – 2 atmospheres with ether.

2-(3-Indolyl)vinyl Isocyanides **1** *and* **4a – c**. *General procedure:* The solution of 584 mg (3.3 mmol) of **2**[3a] in 3 ml of THF was added dropwise to a stirred solution of 839 mg (6.6 mmol) of sodium bis(trimethylsilyl)amide in 5 ml of THF at – 78 °C. The mixture was stirred for 15 min and then treated dropwise with the solution of 3.0 mmol of the 3-indolecarbaldehyde in 30 ml of THF. After stirring for about 20 h at 0 °C 198 mg (3.3 mmol) of acetic acid in 1.5 ml of THF was added. The solvent was removed in vacuo, the residue taken up in 30 ml of ethyl acetate, washed with phosphate buffer pH 7 (15 ml) and H_2O (15 ml), and dried with $MgSO_4$. The solvent was

removed *in vacuo* and the residue chromatographied on silica gel with ether. The pure compounds are extremely unstable and storeable only in solution for short time. Elementary analyses could not be obtained.

(E)- and (Z)-2-(3-Indolyl)vinyl Isocyanide (**1**): With 436 mg (3.0 mmol) of 3-indolecarbaldehyde (**3**). Chromatography on silica gel afforded 110 mg (22%) of *Z*-**1** (R_F = 0.55) and 180 mg (32%) of *E*-**1** (R_F = 0.44). The spectroscopic data for *Z*-**1** are identical with those reported in lit.[1].

E-**1**: ^{1}H NMR (CD_3OD): δ = 7.7–7.0 (m; 5H, 4-H–7-H and β-vinyl-H), 7.41 (s; 1H, 2-H), 6.41 (d, *J* = 14 Hz; α-vinyl-H). – IR (KBr): 3180 (NH), 2120 (NC), 1610 cm^{-1} (C=C). – UV (CH_3OH): λ_{max} = 311 nm (ε = 2.8·10^3). – MS (70 eV): *m/e* = 168 (100%, M^+), 141 (19%, M – HCN), 140 (32%).

2-(5-Bromo-3-indolyl)vinyl Isocyanide (**4a**): With 675 mg (3.0 mmol) of 5-bromo-3-indolecarbaldehyde[6]. Chromatography on silica gel gave 217 mg (29%) of *E*-**4a** (R_F = 0.27) and 135 mg (18%) of *Z*-**4a** (R_F = 0.42).

Z-**4a**: ^{1}H NMR ([D_6]DMSO): δ = 8.05 (s; 2-H), 8.01 (d, *J* = 2 Hz, 4-H), 7.45 and 7.28 (AB spectrum, J_{AB} = 8 Hz, part B was splitted by allylic coupling *J* = 2 Hz; 7-H and 6-H), 7.02 (br. d, *J* = 9 Hz; β-vinyl-H), 6.02 (d, *J* = 9 Hz; α-vinyl-H). – IR (KBr): 3200 (NH), 2110 (NC), 1610 cm^{-1} (C=C).

E-**4a**: ^{1}H NMR ([D_6]DMSO): δ = 7.99 (s; 2-H), 7.81 (br. s; 4-H), 7.1–7.5 (m; 3H, 6-H, 7-H, and β-vinyl-H), 6.65 (d, *J* = 14 Hz; α-vinyl-H). – IR (KBr): 3200 (NH), 2110 (NC), 1615 cm^{-1} (C=C).

2-(5-Methoxy-3-indolyl)vinyl Isocyanide (**4b**): With 525 mg (3.0 mmol) of 5-methoxy-3-indolecarbaldehyde. Chromatography on silica gel afforded 267 mg (45%) of **4b**. *E/Z* = 3:1. – ^{1}H NMR ($CDCl_3$): δ = 8.6 (br.; NH), 8.01 (s; 2-H of *Z*-**4b**), 6.8–7.3 (m; β-vinyl-H), 6.20 (d, *J* = 14 Hz; α-vinyl-H of *E*-**4b**), 5.66 (d, *J* = 9 Hz; α-vinyl-H of *Z*-**4b**), 3.84 (s; CH_3). – IR (KBr): 3200 (NH), 2110 (NC), 1610 cm^{-1} (C=C).

(E)-2-(2-Methyl-3-indolyl)vinyl Isocyanide (**4c**): With 477 mg (3.0 mmol) of 2-methyl-3-indolecarbaldehyde[7]. Chromatography on silica gel afforded 192 mg (35%) of *E*-**4c**. – ^{1}H NMR ([D]$_6$DMSO): δ = 7.8–6.8 (m; 5H), 6.51 (d, *J* = 15 Hz; α-vinyl-H), ≈ 2.4 (s; CH_3, covered by the DMSO signal). – IR (KBr): 3220 (NH), 2100 (NC), 1610 cm^{-1} (C=C).

2-(1-Alkyl-3-indolyl)vinyl Isocyanides **4d–j**: As described above but with 382 mg (3.0 mmol) of sodium bis(trimethylsilyl)amide, stirring for 1.5 h at –78 °C, and work-up without acetic acid.

2-(5-Bromo-1-methyl-3-indolyl)vinyl Isocyanide (**4d**): With 714 mg (3.0 mmol) of 5-bromo-1-methyl-3-indolecarbaldehyde. Chromatography on silica gel gave 36 mg (5%) of *Z*-**4d** (R_F = 0.45) and 463 mg (59%) of *E*-**4d** (R_F = 0.27).

Z-**4d**: ^{1}H NMR ($CDCl_3$): δ = 7.95 (s; 2-H), 7.73 (d, *J* = 2 Hz; 4-H), 7.38 and 7.16 (AB spectrum, J_{AB} = 9 Hz, part A showed allylic coupling *J* = 2 Hz, 6-H and 7-H), 5.68 (d, *J* = 9 Hz; α-vinyl-H), 3.81 (s; CH_3). – IR (KBr): 2110 (NC), 1610 cm^{-1} (C=C).

E-**4d**: ^{1}H NMR ($CDCl_3$): δ = 7.67 (s; 2-H), 7.0–7.5 (m; 3H), 6.93 (d, *J* = 14 Hz; β-vinyl-H), 6.10 (d, *J* = 14 Hz; α-vinyl-H), 3.68 (s; CH_3). – IR (KBr): 2110 (NC), 1615 cm^{-1} (C=C).

$C_{12}H_9BrN_2$ (261.1) Calc. C 55.19 H 3.47 Found C 55.38 H 3.20

2-(1-Methyl-3-indolyl)vinyl Isocyanide (**4e**): With 477 mg (3.0 mmol) of 1-methyl-3-indolecarbaldehyde. Chromatography on silica gel afforded 94 mg (17%) of *Z*-**4e** (R_F = 0.58) and 287 mg (53%) of *E*-**4e** (R_F = 0.49).

Z-**4e**: ^{1}H NMR ($CDCl_3$): δ = 7.92 (s; 2-H), 7.0–7.65 (m; 4H), 6.65 (mc; β-vinyl-H), 5.59 (d, *J* = 9 Hz; α-vinyl-H), 3.83 (s; CH_3). – IR (film): 2110 (NC), 1615 cm^{-1} (C=C).

E-**4e**: ^{1}H NMR (CCl_4): δ = 6.9–7.6 (m; 5H), 6.81 (d, *J* = 15 Hz; β-vinyl-H), 6.05 (d, *J* = 15 Hz; α-vinyl-H), 3.62 (s; CH_3). – IR (film): 2120 (NC), 1620 cm^{-1} (C=C).

$C_{12}H_{10}N_2$ (182.2) Calc. C 79.09 H 5.53 Found C 78.95 H 5.67

2-(5-Methoxy-1-methyl-3-indolyl)vinyl Isocyanide (**4f**): With 567 mg (3.0 mmol) of 5-methoxy-1-methyl-3-indolecarbaldehyde. Chromatography on silica gel gave 42 mg (7%) of *Z*-**4f** (R_F = 0.52) and 405 mg (64%) of *E*/*Z* mixture (3:1); R_F (*E*-**4f**) = 0.40. – ^{1}H NMR ($CDCl_3$): δ = 7.94 (s; 2-H of *Z*-**4f**), 6.8–7.3 (m; indolyl-H and β-vinyl-H of *E*-**4f**), 6.65 (mc; β-vinyl-H of *Z*-**4f**), 6.17 (d, *J* = 14 Hz; α-vinyl-H of *E*-**4f**), 5.62 (d, *J* = 9 Hz; α-vinyl-H of *Z*-**4f**), 3.85 (s; OCH_3), 3.78 and 3.72 (each s; CH_3 of *Z*- and *E*-**4f**). – IR (film): 2110 (NC), 1615 cm^{-1} (C=C).

$C_{13}H_{12}N_2O$ (212.2) Calc. C 73.56 H 5.70 Found C 73.74 H 5.73

2-(1,2-Dimethyl-3-indolyl)vinyl Isocyanide (**4g**): With 519 mg (3.0 mmol) of 1,2-dimethyl-3-indolecarbaldehyde. Chromatography on silica gel afforded 453 mg (77%) of **4g**, *E*/*Z* = 3:1. – ^{1}H NMR (CCl_4): δ = 7.5–6.9 (m; indolyl-H), 6.91 and 6.13 (d, *J* = 14 Hz; β- and α-vinyl-H of *E*-**4g**), 6.5 (br.) and 5.70 (each d, *J* = 9 Hz; β- and α-vinyl-H of *Z*-**4g**), 3.56 (s; NCH_3), 2.35 and 2.32 (each s; CH_3). – IR (film): 2110 (NC), 1615 cm^{-1} (C=C).

$C_{13}H_{12}N_2$ (196.2) Calc. C 79.56 H 6.17 Found C 79.48 H 6.15

2-(1-Ethyl-3-indolyl)vinyl Isocyanide (**4h**): With 519 mg (3.0 mmol) of 1-ethyl-3-indolecarbaldehyde. Chromatography on silica gel afforded 78 mg (13%) of *Z*-**4h** (R_F = 0.55) and 330 mg (56%) of *E*-**4h** (R_F = 0.14).

Z-**4h**: ^{1}H NMR (CCl_4): δ = 7.96 (s; 2-H), 7.0–7.6 (m; indolyl-H), 6.60 (br. d, *J* = 9 Hz; β-vinyl-H), 5.55 (d, *J* = 9 Hz; α-vinyl-H), 4.18 and 1.51 (q and t, *J* = 8 Hz; CH_2, CH_3). – IR (film): 2110 (NC), 1615 cm^{-1} (C=C).

E-**4h**: ^{1}H NMR (CCl_4): δ = 7.1–7.6 (m; 4H, indolyl-H), 7.06 (s; 2-H), 6.95 and 6.15 (each d, *J* = 14 Hz; β- and α-vinyl-H), 4.01 and 1.38 (q and t, *J* = 7 Hz; CH_2, CH_3). – IR (film): 2110 (NC), 1620 cm^{-1} (C=C).

$C_{13}H_{12}N_2$ (196.2) Calc. C 79.56 H 6.17 Found C 79.55 H 6.17

2-(1-Benzyl-3-indolyl)vinyl Isocyanide (**4i**): With 7.02 mg (3.0 mmol) of 1-benzyl-3-indolecarbaldehyde. Chromatography on silica gel afforded 573 mg (74%) of **4i**, *E*/*Z* = 6:1. – ^{1}H NMR (CCl_4): δ = 7.94 (s; 2-H of *Z*-**4i**), 6.9–7.6 (m; arom.-H), 6.78 and 6.05 (each d, *J* = 14 Hz; β- and α-vinyl-H of *E*-**4i**), 6.58 (br), 5.50 (each d, *J* = 9 Hz; β- and α-vinyl-H of *Z*-**4i**), 5.11 and 5.07 (each s; CH_2 of *Z*- and *E*-**4i**). – IR (film): 2110 (NC), 1620 cm^{-1} (C=C).

$C_{18}H_{14}N_2$ (258.3) Calc. C 83.69 H 5.46 Found C 83.51 H 5.58

1-(Diethoxyphosphoryl)-3-indolecarbaldehyde: The solution of 5.18 g (30 mmol) of diethyl chlorophosphate in 10 ml of THF was added dropwise to 4.36 g (30 mmol) of 3-indolecarbaldehyde (**3**) and 3.7 g (30 mmol) of potassium *tert*-butoxide in 50 ml of THF at 5 °C. After stirring for 1 h at room temperature the solvens was removed *in vacuo*. The residue was taken up in 40 ml of ether, washed with water (20 ml) and saturated NaCl solution, and dried with $MgSO_4$. The ether was removed *in vacuo* and the residue recrystallized from ethyl acetate. Yield 7.05 g (84%), m.p. 57 °C. – ^{1}H NMR ($CDCl_3$): δ = 9.95 (s; CHO), 7.0–8.2 (m; indolyl-H), 3.7–4.4 (m; CH_2), 1.23 (t, *J* = 7 Hz; CH_3). – IR (KBr): 1660 cm^{-1} (C=O).

$C_{13}H_{16}NO_4P$ (281.2) Calc. C 55.52 H 5.73 Found C 55.80 H 5.71

(E)-2-[1-(Diethoxyphosphoryl)-3-indolyl]vinyl Isocyanide (**4j**): With 843 mg (3.0 mmol) of 1-(diethoxyphosphoryl)-3-indolecarbaldehyde (see above). Yield 490 mg (54%) of *E*-**4j** (R_F =

0.29). – ^{1}H NMR (CCl_4): δ = 7.8 – 7.5 and 7.15 – 7.35 (m; indolyl-H), 7.00 and 6.38 (each d, J = 14 Hz; β- and α-vinyl-H), 3.8 – 4.4 (m; CH_2), 1.29 (t, J = 7 Hz; CH_3). – IR (film): 2110 (NC), 1625 cm^{-1} (C=C).

$C_{15}H_{17}N_2O_3P$ (304.3) Calc. C 59.20 H 5.63 Found C 59.06 H 5.69

4k – m were prepared as described above, but with 30% excess of **2**.

2-Phenylvinyl Isocyanide (**4k**): With 318 mg (3.0 mmol) of benzaldehyde. Chromatography on silica gel gave 294 mg (72%) of **4k**, E/Z = 10:1. – ^{1}H NMR ($CDCl_3$): δ = 7.1 – 7.75 (m; C_6H_5 and β-vinyl-H of *Z*-**4k**), 6.85 (br.) and 6.19 (each d, J = 15 Hz; β- and α-vinyl-H of *E*-**4k**), 5.76 (d, J = 9 Hz; α-vinyl-H of *Z*-**4k**). – IR (film): 2110 cm^{-1} (NC); identical with an authentic sample[3a].

2-(4-Methoxyphenyl)vinyl Isocyanide (**4l**): With 408 mg (3.0 mmol) of 4-methoxybenzaldehyde. Yield 380 mg (80%) of **4l**, E/Z = 4:1; R_F = 0.56. – ^{1}H NMR (CCl_4): δ = 6.7 – 7.7 (m; C_6H_4 and β-vinyl-H), 6.06 (d, J = 15 Hz; α-vinyl-H of *E*-**4l**), 5.64 (d, J = 9 Hz; α-vinyl-H of *Z*-**4l**), 3.76 (s; CH_3). – IR (film): 2100 (NC), 1590 cm^{-1} (C=C).

$C_{10}H_9NO$ (159.2) Calc. C 75.44 H 5.70 Found C 75.40 H 5.73

(E)-2-Thienylvinyl Isocyanide (**4m**): With 337 mg (3.0 mmol) of 3-thiophenecarbaldehyde. Yield 304 mg (75%) of *E*-**4m**. R_F = 0.65. – ^{1}H NMR (CCl_4): δ = 7.0 – 7.4 (m; thienyl-H), 6.88 and 6.13 (each d, J = 15 Hz; β- and α-vinyl-H). – IR (film): 2115 (NC), 1615 cm^{-1} (C=C).

C_7H_5NS (135.2) Calc. C 62.19 H 3.73 Found C 61.98 H 3.61

The α-isocyanoacrylic esters **5a – c** and **5h – j** were prepared as described in lit.[4a-c]. For **5d – g** see lit.[3b] and for **5k** lit.[8].

N-[2-(3-Indolyl)vinyl]formamide **6a** and **6b**: The mixture of 1.0 mmol of **1** (or of **4e**), 7 ml of methanol, and 0.7 ml of water was stirred with 126 mg (1.0 mmol) of oxalic acid dihydrate for about 20 h at 0 °C. The solvent was removed *in vacuo*, the residue was taken up in 25 ml of ethyl acetate, washed with water, $NaHCO_3$, and saturated NaCl solution and dried with $MgSO_4$. The solvent was removed *in vacuo* and the residue purified by chromatography on silica gel.

(E)-N-[2-(3-Indolyl)vinyl]formamide (**6a**): With 168 mg (1.0 mmol) of *E*-**1**. Chromatography on silica gel with ethyl acetate/petroleum ether (3:1) afforded 151 mg (81%) of *E*-**6a**, m.p. 165 °C; R_F = 0.22. – ^{1}H NMR (CD_3OD): δ = 7.65 (s; CHO), 6.6 – 7.4 (m; indolyl-H and β-vinyl-H), 6.09 (d, J = 15 Hz; α-vinyl-H). – IR (KBr): 3220 (NH), 1650 cm^{-1} (C=O).

$C_{11}H_{10}N_2O$ (186.2) Calc. C 70.95 H 5.41 Found C 71.02 H 5.42

(E)-N-[2-(1-Methyl-3-indolyl)vinyl]formamide (**6b**): With 182 mg (1.0 mmol) of *E*-**4e**. Chromatography on silica gel with ether gave 145 mg (73%) of *E*-**6b** with R_F = 0.12. R_F (ethyl acetate/petroleum ether 3:1) = 0.25. – ^{1}H NMR ($CDCl_3$): δ = 8.4 (br.; NH), 8.02 (s; CHO), 6.9 – 7.9 (m; indolyl-H and β-vinyl-H), 6.30 (d, J = 15 Hz; α-vinyl-H), 3.42 (s; CH_3). – IR (KBr): 3220 (NH), 1650 cm^{-1} (C=O).

$C_{12}H_{12}N_2O$ (200.2) Calc. C 71.97 H 6.04 Found C 71.83 H 6.04

6c was prepared as described in lit.[4a].

Biological Tests

Antimicrobial activities were determined by a disc diffusion test on agar plates. 6-mm discs and test solutions containing 1 mg/ml in methanol were used. The agar plates were incubated at 37 °C for 24 hours (results of Table 1 and 2).

Table 1. Antimicrobial Activities of the Vinyl Isocyanides **1** and **4**

Comp.	Conf.	% Yield	Zone diameter (mm)[a,b] *Escherichia coli*	*Bacillus subtilis*	*Mucor muhei* TÜ 284
1	*Z*	22	25	44	33
	E	32	18	41	38
4a	*Z*	18	21	40	
	E	29	18	27	
4b	*E*/*Z* = 3:1	45	21	23	
4c	*E*	35	14	28	
4d	*Z*	5	17	31	
	E	59	15	27	27
4e	*Z*	17	32	45	80
	E	53	22	36	47
4f	*E*/*Z* = 3:1	64	17	30	38
4g	*E*/*Z* = 3:1	77	20	30	44
4h	*Z*	13	33	32	65
	E	56	23	33	61
4i	*E*/*Z* = 6:1	74	15	21	21
4j	*E*	54	trace	26	25
4k	*E*/*Z* = 10:1	72	–	–	55
4l	*E*/*Z* = 4:1	80	–	26	60
4m	*E*	75	–	31	>85

[a] Disc diffusion test (6 mm discs); 1 mg **1** or **4**/ml. – [b] – : No activity.

Table 2. Antimicrobial Activities of the α-Isocyanoacrylates **5** and of the *N*-Vinylformamides **6**

Comp.	Zone diameter (mm)[a,b] *Escherichia coli*	*Bacillus subtilis*	*Mucor muhei* TÜ 284
5a	51	–	85
5b	65	–	>85
5c	27	24	38
5d	21	36	56
5e	>85	–	>85
5f	53	50	74
5g	20	27	30
5h	14	12	29
5i	–	–	–
5j	–	–	trace
5k	–	–	13
6a	–	–	–
6b	–	–	–
6c	–	–	–
Penicillin V, sodium salt	17	33	–

[a] Disc diffusion test (6 mm discs); 1 mg **5** or **6**/ml. – [b] – : No activity.

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