Articles

Synthesis and Antifungal Activity of (*E*)-*N*-(6,6-Dimethyl-2-hepten-4-ynyl)-*N*-methyl-1-naphthalenemethanamine (SF 86-327) and Related Allylamine Derivatives with Enhanced Oral Activity

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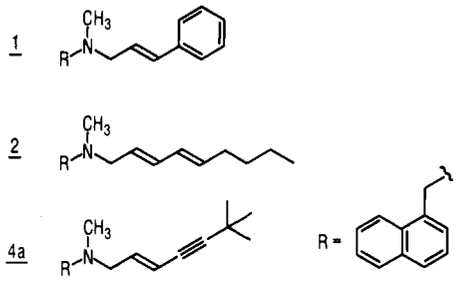
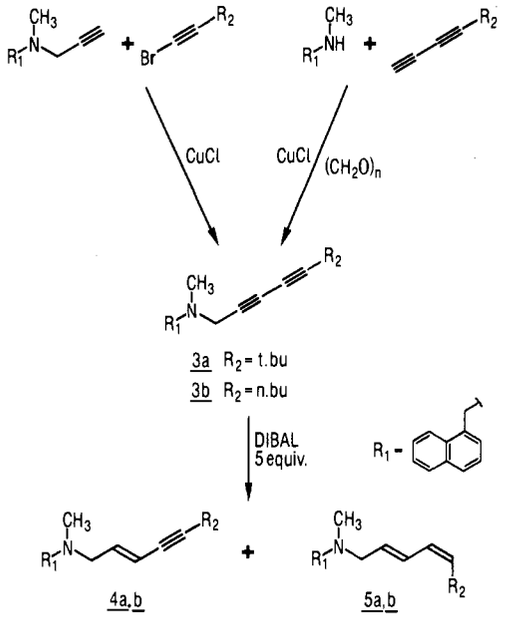
The allylamine derivatives are a new class of synthetic antifungal agents inhibiting fungal squalene epoxidase. A new subclass, which features an acetylene group conjugated with the allylamine double bond, is characterized by enhanced antifungal activity, especially on oral treatment of guinea pig dermatophytoses. Increased branching of the alkyl group next to the triple bond led to the *tert*-butylacetylene derivative SF 86-327, a compound with strikingly increased activity in vitro and in vivo, which is now under clinical evaluation. Versatile synthetic routes, comparative biological data, and structure–activity relationships are presented.

Recently we reported on a new class of synthetic antifungal agents, characterized by an allylamine function as the essential structural feature.[1] The antifungal activity of naftifine (**1**),[2-4] the first member of this type, was discovered during routine screening, and numerous clinical studies have already proved its high efficacy as a topical antimycotic.[5] An intensive derivatization program based on naftifine led to the synthesis of **4a** (SF 86-327), in which the allylamine double bond is conjugated with a *tert*-butylacetylene group. Compound **4a** was found to be highly active in vitro against a wide range of fungi and significantly superior to standard reference drugs such as ketoconazole, griseofulvin, econazole, and tolnaftate in the oral and topical treatment of guinea pig dermatophytoses.[1] Compound **4a** is a powerful and specific inhibitor of squalene epoxidase in *Candida albicans*, a mode of action distinct from other antimycotics.[1]



In an earlier study on structure–activity relationships within the allylamines, we investigated the effect of replacing the cinnamyl group in naftifine by a series of alk(en)yl groups. An analogue with a 2,4-alkadienyl side chain of suitable length (**2**) was shown to have antimycotic properties comparable to those of naftifine, while analogues with a higher or lower number of double bonds were less active.[6]

Scheme I



The continuation of this work, leading to **4a**, is described in this paper, together with synthetic routes and comparative biological data.[7]

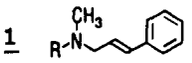
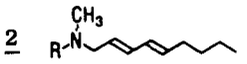
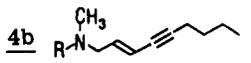
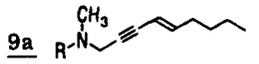
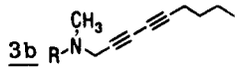
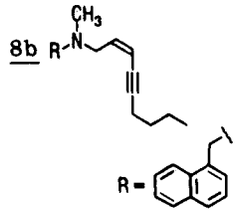
Chemistry. Compound **2** was synthesized by reduction of the imine formed from *trans,trans*-2,4-nonadienal and 1-naphthalenemethanamine, followed by reductive methylation.

Two versatile routes adaptable to a broad derivatization program were developed for the synthesis of alk-2-en-4-ynylamines **4** and **8**. Route 1 exploits our recent finding[8] that tertiary 2-propynylamines are selectively reduced to *trans*-allylamines by Dibal (diisobutylaluminum hydride) in toluene, in contrast to the well-known cis reduction of simple acetylenes.[9] Treatment of conjugated diynes **3a,b** with excess Dibal resulted in the stereoselective formation of *trans*-enynes **4a,b** and *trans,cis*-dienes **5a,b**, which underlines the importance of the neighboring amine partic-

(1) Petranyi, G.; Ryder, N. S.; Stütz, A. *Science* **1984**, *224*, 1239.
(2) Georgopoulos, A.; Petranyi, G.; Mieth, H.; Drews, J. *Antimicrob. Agents Chemother.* **1981**, *19*, 386.
(3) Petranyi, G.; Georgopoulos, A.; Mieth, H. *Antimicrob. Agents Chemother.* **1981**, *19*, 390.
(4) Berney, D.; Schuh, K. *Helv. Chim. Acta* **1978**, 1262.
(5) For example, see: Ganzinger, U.; Stephen, A.; Gumhold, G. *Clin. Trials J.* **1982**, 342. Hantschke, D.; Reichenberger, M. *Mykosen* **1980**, *23*, 657.
(6) Stütz, A.; Petranyi, G. *Curr. Chemother. Immunother. Proc. Int. Congr. Chemother. 12th* **1982**, 1021.
(7) Part of this paper has already been presented at the 13th International Congress of Chemotherapy, Vienna, Austria, 1983, Poster Session 4.8/4-1 and 4.8/4-2.
(8) Granitzer, W.; Stütz, A. *Tetrahedron Lett.* **1979**, *34*, 3145. Stütz, A.; Granitzer, W.; Roth, S. *Tetrahedron*, in press.
(9) Winterfeldt, E. *Synthesis* **1975**, 617.

0022-2623/84/1827-1539$01.50/0

Table I. In Vitro and in Vivo Antimycotic Activity of Allylamine Derivatives

	MIC (mg/l)					IN VIVO ACTIVITY (% myc. cure)				
						TOPICAL		ORAL		
	Trich. ment.	*Epid. fl.*	*Micr. can.*	*Spor. sch.*	*Cand. par.*	0.125%	0,5%	37.5 [+]	75	150
1 	0.05	0.2	0.1	1.6	1.6	35	65	-	-	48
2 	0.05	0.2	0.1	3.1	1.6	40	69	-	-	43
4b 	0.01	0.01	0.01	1.6	0.4	83	100	83	100	100
9a 	0.2	1.6	0.2	>100	>100					
3b 	0.2	3.1	0.8	100	100					
8b 	0.2	100	0.2	50	100					

[+] mg/kg/day

ipation. The relative yields of mono- and direduction products were about equal for R_2 = *n*-butyl (compounds **4b** and **5b**), whereas for R_2 = *tert*-butyl monoreduced **4a** predominated. Diynes **3a,b** were obtained either by Cadiot–Chodkiewicz coupling of *N*-methyl-*N*-2-propynyl-1-naphthalenemethanamine and bromoacetylenes or by a Mannich reaction with 1,3-diynes as the acidic component (Scheme I).

In route 2, 1-alkynes were lithiated and reacted by 1,2-addition with acrolein to give the secondary alcohols **6a–c**. They were converted to a mixture of stereoisomeric allylbromides **7a,c** ($E/Z \sim 3:1$) by treatment with aqueous HBr. After N-alkylation the *trans*- and *cis*-enynes **4a–c** and **8a–c** were obtained and separated by chromatography or by selective crystallization of the trans isomer as the hydrochloride (Scheme II).

Mannich reaction of an E/Z mixture of 3-octen-1-yne with *N*-methyl-1-naphthalenemethanamine and paraformaldehyde, catalyzed by CuCl, furnished the inverted ynene **9a**, together with its *Z* isomer **9b**.

The stereochemistry of the various double bonds was deduced from the NMR spectra.

Mycology. The antifungal activity in vitro of the allylamines was investigated against isolates of *Trichophyton mentagrophytes* (Trich. ment.), *Epidermophyton floccosum* (Epid. fl.), *Microsporum canis* (Micr. can.), *Sporothrix schenkii* (Spor. sch.), *Aspergillus fumigatus* (Asp. fum.), *Candida albicans* (Cand. alb.), and *Candida parapsilosis* (Cand. par.). Minimum inhibitory concentrations (MIC) were determined using Sabouraud's dextrose broth (pH 6.5) in test tubes. The test compounds were dissolved in Me_2SO and serially diluted with the growth media. The growth control for yeasts was read after 48 h, for moulds after 72 h, and for dimorphic fungi and all dermatophytes after 7 days of incubation at 30 °C. The MIC was defined as that substance concentration at which no macroscopic signs of fungal growth were detectable.

The activity in vivo was determined by oral and topical treatment of guinea pig dermatophytosis caused by *Trichophyton mentagrophytes*. The tests were carried out with use of 8–10 guinea pigs at each dose level. The backs (lumbar region) of the animals were shorn and then inoculated with 0.1 mL of Sabouraud's 2% dextrose broth containing 10^6 cfu of *T. mentagrophytes* over a circular area 3.5 cm in diameter.

For oral treatment, the test compound was dissolved in miglyol 812 (Dynamit-Nobel; mixture of triglycerides of saturated fatty acids), and 0.5 mL each of the various doses were administered by stomach tube. Treatment was once daily for 9 consecutive days, starting on the day of inoculation. For topical treatment, 0.4 mL of the test compound solution (PEG 400/ethanol = 75/25, v/v) was spread over the infected skin area of the animals, which were treated once daily for 7 consecutive days, starting 48 h after inoculation. The mycological status was assessed on the first (oral administration) or third day (topical administration) after the last treatment, by culturing hairs from the infected lesions. Following incubation, cultures were evaluated microscopically for fungal growth in the region of hair roots.[10]

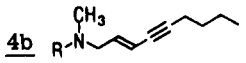
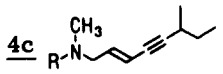
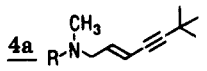
Results and Discussion

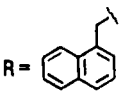
As shown in Table I, the antifungal activity of compound **2** with an (*E,E*)-2,4-alkadienyl side chain is comparable to that of naftifine (**1**) in vitro and in vivo. Replacement of the Δ^4-double bond by an triple bond (compound **4b**) was found to enhance activity both in vitro and in vivo with a particularly striking improvement after oral application. A trans double bond in the enyne system is a rigorous stereochemical requirement for this effect. The corresponding cis isomer (compound **8b**) has significantly lower activity.[11] In contrast to **4b**, a compound with an inverted enyne unit **9b** is much less active as is an analogue **3b** with two conjugated acetylene groups.

Increased branching of the alkyl group next to the acetylene function (Table II) led to a further improvement

(10) Petranyi, G.; Leitner, I.; Mieth, H. *Sabouraudia* **1982**, *20*, 101.
(11) The *cis*-enynes **8a,c** are also much less active than the *trans*-enynes **4a,c**.

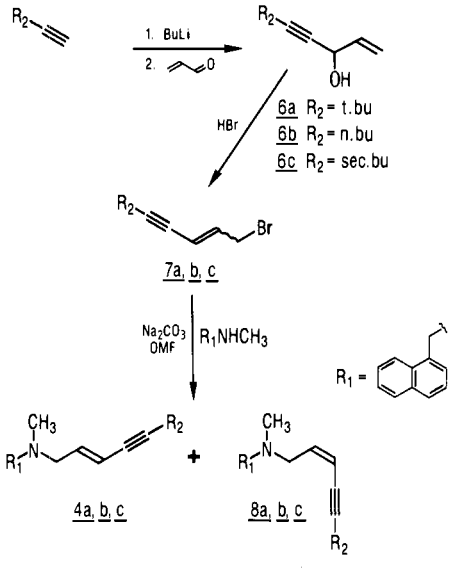
Table II. In Vitro and in Vivo Antimycotic Activity of Allylamines with an Enyne Side Chain

	MIC (mg/l)							ORAL ACTIVITY (% myc. cure)	
	Trich. ment.	*Epid. fl.*	*Micr. can.*	*Spor. sch.*	*Asp. fum.*	*Cand. alb.*	*Cand. par.*	5[+]	10
4b 	0.01	0.01	0.01	1.6	100	100	0.4	0	15
4c 	0.01	0.006	0.006	0.8	100	100	0.4	23	75
4a 	0.006	0.006	0.006	0.4	0.8	25	0.4	98	100

R = 

[+] mg/kg/day

Scheme II



of about 1 order of magnitude in oral activity in compound **4a**.

As has been previously reported,[1] **4a** effected 100% myc. cure at a dose level of 6 mg/kg of body weight while on direct comparison ketoconazole and griseofulvin needed 60–80 mg/kg of body weight for mycological cure. On topical application, a 0.03–0.06% solution of **4a**, completely cured guinea pigs infected with *Trichophyton mentagrophytes*, again superior to the standards econazole and tolnaftate by more than 1 order of magnitude.

Inspection of the primary results in vitro shows that activity against *Aspergillus fumigatus* and *Candida albicans* is also strongly dependent on the degree of branching. The tertiary butyl group is a prerequisite for activity against these two organisms, thus resulting in a valuable expansion of the antifungal spectrum (Table II).

The conjugated *trans*-enyne group, which has been shown to be a structural modification important for enhancement of antimycotic activity, especially on oral application, is to our knowledge a novel structural feature in medicinal chemistry. Within this new series, **4a** clearly demonstrated superior activity and was selected for further development. Detailed reports on its biological activity, pharmacological behavior, and clinical results will be reported elsewhere.[12]

(12) The first presentation of preclinical and clinical data was at the 13th International Congress of Chemotherapy, Vienna, Austria, 1983, Poster Session 4.8/4 and Symposium 49/1-5.

Experimental Section

Melting points were determined on a Reichert Thermovar microscope and are not corrected. The compounds were identified by IR spectra on a Perkin-Elmer spectrophotometer and ^{1}H NMR data recorded in $CDCl_3$ at 90 MHz (Bruker WH 90) or 250 MHz (Bruker WM 250) with $(CH_3)_4Si$ as internal standard. Mass spectra were recorded on a MAT 311A instrument with EI ion source (70 eV and 250 °C) and direct inlet system at the University of Vienna.

The purity of the compounds was checked by GLC (Siemens Sichromat 1) using quartz capillaries (stat. phase OV-101) or high-performance liquid chromatography (pump: Waters M 6000) on a column of RP 18, 10 μm (Partisil ODS-10), with a water/acetonitrile gradient and a Schoeffel SF 770 UV detector (270 nm).

Thin-layer chromatography was performed on silica gel 60 F_{254} (Merck), and the spots were made visible by a UV lamp or iodine vapor. Column chromatography was done on silica gel 60 (0.040–0.063 mm, Merck) under pressures of 3–5 bars.

Elemental analyses were performed by the microanalytical laboratory at the University of Vienna.

N-Methyl-*N*-2-propynyl-1-naphthalenemethanamine, *N*-methyl-1-naphthalenemethanamine, and 1-naphthalenemethanamine were prepared according to the literature.[13-15] Naftifine [(*E*)-*N*-Methyl-*N*-(3-phenyl-2-propenyl)-1-naphthalenemethanamine] was prepared by N-alkylation of *N*-methyl-1-naphthalenemethanamine with cinnamyl bromide.[14]

***N*-(6,6-Dimethyl-2,4-heptadiynyl)-*N*-methyl-1-naphthalenemethanamine (3a).** A mixture of *N*-methyl-1-naphthalenemethanamine (1 g, 5.8 mmol), paraformaldehyde (0.17 g, 5.8 mmol), *tert*-butylbutadiyne[16] (0.74 g, 7 mmol), and CuCl (0.075 g, 0.58 mmol) in dry dioxane (20 mL) was heated to reflux for 1 h. After cooling, the solvent was evaporated and the residue treated with ether and brine. The organic phase was separated, dried, concentrated in vacuo, and chromatographed (toluene/ethyl acetate = 95/5). Compound **3a** (1.19 g, 71%) was obtained as an oil, which crystallized on standing in a refrigerator: mp 78–81 °C; IR 2240 cm^{-1} (C≡C); NMR δ 8.1–8.25 (m, 1 H), 7.6–7.85 (m, 2 H), 7.2–7.5 (m, 4 H), 3.92 (s, Ar CH_2N), 3.33 (s, $NCH_2C\equiv$), 2.35 (s, NCH_3), 1.22 (s, 9 H); mp (hydrochloride) 175–76 °C (2-propanol). Anal. ($C_{21}H_{23}N$·HCl) C, H, N, Cl. Compound **3a** was also prepared as described for **3b** in 79% yield.

***N*-Methyl-*N*-2,4-nonadiynyl-1-naphthalenemethanamine (3b).** 1-Bromo-1-hexyne (8.25 g, 51 mmol) was added dropwise under argon to a stirred mixture of *N*-methyl-*N*-2-propynyl-1-naphthalenemethanamine (16 g, 76 mmol), CuCl (0.25 g), NH_2-OH·HCl (0.51 g), 70% aqueous ethylamine (20 mL), and methanol (25 mL) at a temperature between 14 and 19 °C. After the mixture was stirred overnight, NaCN (1 g) was added. The mixture was

(13) *Span.* 281, 171; *Chem. Abstr.* **1963**, *60*, 2904d.
(14) Berney, D. Ger. Offen. 2809211; *Chem. Abstr.* **1980**, *92*, 58500d.
(15) Blicke, F. F.; Maxwell, C. E. *J. Am. Chem. Soc.* **1939**, *61*, 1780.
(16) Brandsma, L. "Preparative Acetylenic Chemistry"; Elsevier: Amsterdam, 1971; p 155.

poured into water and extracted three times with ether. After washing and drying, the ether extract was concentrated in vacuo and the residue chromatographed (toluene/ethyl acetate = 95/5) to give **3b** (11.33 g, 76.8%, based on 1-bromo-1-hexyne) as a viscous oil: IR 2240 cm^{-1} (C≡C); NMR δ 3.97 (s, Ar CH_2N), 3.37 (s, $NCH_2C≡$), 2.40 (s, NCH_3), 2.2–2.4 (m, $≡CCH_2$), 1.2–1.8 (m, 4 H), 0.8–1.05 (pst, 3 H); MS, *m/e* 289.

Reduction of Diynes 3a and 3b with Dibal. (1) **(*E*)-*N*-Methyl-*N*-2-nonen-4-ynyl-1-naphthalenemethanamine (4b) and *N*-Methyl-*N*-2(*E*),4(*Z*)-nonadienyl-1-naphthalenemethanamine (5b).** A solution of diisobutylaluminum hydride (Dibal; 720 mL of a 1.2 M solution, 0.865 mol) in toluene was added dropwise to a solution of **3b** (50 g, 0.173 mol) in dry toluene (300 mL) within about 1 h under argon. A slightly exothermic reaction occurred during addition of the reagent, the internal temperature rising to about 40 °C. The reaction solution was kept at 40 °C overnight. Excess reagent was cautiously destroyed with 2 N NaOH and after addition of further 2 N NaOH the toluene phase was separated. After extraction of the aqueous phase with ether, the combined organic extracts were washed, dried, and evaporated to dryness. GC analysis showed the residue (48 g) to consist of a mixture of **4b** (52.5%) and **5b** (42.5%), which were separated by chromatography (toluene/ethyl acetate = 95:5). Compound **4b** (22,1 g, 42.9 %), followed by **5b** (16.17 g, 31.8%), were isolated in pure form as colourless oils.

Compound **4b**: NMR δ 6.17 (dt, *J* = 15 and 2 × 6.5 Hz, (*E*)-CH_2CH=CH), 5.67 (d, *J* = 15 Hz, (*Z*)-CH=CHC≡), 3.13 (d, *J* = 6.5 Hz, NCH_2C=); mp (hydrochloride) 118–121 °C (2-propanol/diethyl ether). Anal. ($C_{21}H_{25}N$·HCl) C, H, N, Cl.

Compound **5b**: NMR for NCH_2-(*E*)-CH_α=CH_β-(*Z*)-CH_γ=$CH_\delta CH_2$, δ 6.53 (H_β), 6.02 (H_γ), 5.80 (H_α), 5.40 (H_δ); $J_{H_\alpha H_\beta}$ = 15 Hz, $J_{H_\alpha CH_2N}$ = 6.5 Hz, $J_{H_\beta CH_2N}$ = 1.5 Hz, $J_{H_\beta H_\gamma}$ = 11 Hz, $J_{H_\gamma H_\delta}$ = 11 Hz, $J_{H_\gamma CH_2}$ = 1.5 Hz, $J_{H_\delta CH_2}$ = 7 Hz; 3.9 (s, NCH_3), 2.0–2.3 (m, $=CCH_2$); MS, *m/e* 293.

(2) Reduction of **3a** (0.579 g, 2 mmol) as described for **3b** resulted in the isolation of **4a** (270 mg, 46.3%) and **N-(6,6-dimethyl-2(*E*),4(*Z*)-heptadienyl)-*N*-methyl-1-naphthalenemethanamine (5a)** (110 mg, 19%, oil): NMR for NCH_2-(*E*)-CH_α=CH_β-(*Z*)-CH_γ=CH_δ, δ 6.74 (H_β), 5.87 (H_γ), 5.74 (H_α), 5.36 (H_δ); $J_{H_\alpha H_\beta}$ = 15 Hz, $J_{H_\alpha CH_2N}$ = 6.5 Hz, $J_{H_\beta CH_2N}$ = 1.5 Hz, $J_{H_\beta H_\gamma}$ = 11 Hz, $J_{H_\gamma H_\delta}$ = 11 Hz; 3.9 (s, Ar CH_2N), 3.17 (dd, NCH_2), 2.22 (s, NCH_3), 1.16 (*t*-Bu); MS, *m/e* 293.

6,6-Dimethyl-1-hepten-4-yn-3-ol (6a). 3,3-Dimethyl-1-butyne (300 g, 3.65 mol) was dissolved in tetrahydrofuran (3 L, freshly distilled over $LiAlH_4$) and a 15% solution of *n*-butyllithium (2.4 L, 3.84 mol) in hexane was added at a temperature between −15 and −20 °C under inert gas within 2 h. The solution was then cooled to −70 °C and acrolein (225.4 g, 4.02 mol), dissolved in tetrahydrofuran (600 mL), added within 3 h. After the mixture was stirred overnight at room temperature, saturated aqueous NH_4Cl was added and the reaction mixture neutralized with dilute H_2SO_4. Most of the tetrahydrofuran was evaporated in vacuo and the residue extracted several times with diethyl ether. The organic phase was washed with brine, dried (Na_2SO_4), and evaporated. The oily residue (586 g, 116%, GC purity 72.6%) was distilled through a 75-cm Vigreux column and **6a** (322.8 g, 64%, GC purity 99.3%) obtained at 73–75 °C (12 mm). **6a**: n^{20}_D 1.453; NMR δ 5.92 (ddd, *J* = 17, 10, and 5 Hz, vinyl H), 5.35 (dm, *J* = 16 Hz, vinyl H), 5.12 (dm, *J* = 10 Hz, vinyl H), 4.8 (dm, *J* = 5 Hz, $CHOH$), 2.1 (O*H*), 1.18 (s, 9 H). Anal. ($C_9H_{14}O$) C, H.

1-Nonen-4-yn-3-ol (6b) was prepared by the above procedure starting from 1-hexyne (100 g, 1.22 mol): yield of **6b** after distillation 111 g (66%); bp 42–43 °C (0.1 mm); NMR δ 6.0 (ddd, *J* = 17, 10, and 5 Hz, vinyl H), 5.4 (dm, *J* = 17 Hz, 1 H), 5.2 (dm, *J* = 10 Hz, 1 H), 4.85 (m, *CH*OH), 2.2 (m, 2 H), 2.05 (OH), 1.2–1.6 (dm, 4 H), 0.9 (pst, 3 H). Anal. ($C_9H_{14}O$) C, H.

6-Methyl-1-octen-4-yn-3-ol (6c) was prepared by the above procedure starting from 3-methyl-1-pentyne (8 g, 97 mmol): yield of **6c** after distillation 9.4 g (70%); bp 75–80 °C (12 mm); n^{20}_D 1.461; NMR δ 6.0 (ddd, *J* = 17, 10, and 5 Hz, vinyl H), 5.45 (dm, *J* = 17 Hz, vinyl H), 5.2 (dm, *J* = 10 Hz, vinyl H), 4.9 (m, *CH*OH), 2.44 (sext, *J* = 7 Hz, 1 H), 2.1 (OH), 1.48 (quint, *J* = 7 Hz, 2 H), 1.18 (d, *J* = 7 Hz, 3 H), 1.0 (t, *J* = 7 Hz, 3 H). Anal. ($C_9H_{14}O$) C, H.

1-Bromo-6,6-dimethyl-2-hepten-4-yne (7a). HBr (48%, 1.5 L) and PBr_3 (300 g) were vigorously stirred at 40 °C, until a homogeneous mixture was obtained. A solution of **6a** (422 g, 3.05 mol) in ethanol (500 mL) was added at 10 °C and stirred until the reaction was complete (1–2 h). The reaction mixture was poured onto ice and extracted several times with hexane. The organic phase was washed neutral, dried (Na_2SO_4), and concentrated in vacuo. NMR spectroscopy and TLC (toluene/ethyl acetate = 95/5) showed that the yellow oily product (601 g, 98%) comprised a 3:1 mixture of *trans*- and *cis*-**7a**, which was taken directly for N-alkylation. **7a**: NMR δ 5.5–6.4 (m, *CH*=*CH*) [4.15 (d, *J* = 8 Hz) and 3.95 (d, *J* = 8 Hz), in ratio 1:3, =CHCH_2Br], 1.20 (*t*-Bu).

1-Bromo-2-nonen-4-yne (7b) was prepared as described above starting from **6b** (20 g, 145 mmol). After workup an *E*/*Z* mixture (3/1) of oily **7b** (27.2 g, 94%) was obtained and used directly for N-alkylation. **7b**: NMR δ 5.4–6.4 (m, *CH*=*CH*) [4.15 (d, *J* = 8 Hz) and 3.95 (d, *J* = 8 Hz) in ratio 1:3, =CHCH_2Br], 2.1–2.6 (br, $≡CCH_2$).

1-Bromo-6-methyl-2-octen-4-yne (7c) was prepared as described above starting from **6c** (4.92 g, 35.6 mmol). After workup an *E*/*Z* mixture (3/1) of oily **7c** (6.55 g, 92%) was obtained and used directly for N-alkylation: NMR δ 5.4–6.4 (m, *CH*=*CH*), 4.15 (d, *J* = 8 Hz) and 3.95 (d, *J* = 8 Hz) in ratio 1:3 (=CHCH_2Br), 2.2–2.7 (m, ≡CCH).

(*E*)-*N*-(6,6-Dimethyl-2-hepten-4-ynyl)-*N*-methyl-1-naphthalenemethanamine (4a) and Its *Z* Isomer 8a. Compound **7a** (601 g, 3 mol, *E*/*Z* = 3/1) was added dropwise with cooling with ice to a mixture of *N*-methyl-1-naphthalenemethanamine (536.7 g, 3.13 mol), Na_2CO_3 (332 g, 3.13 mol) and dimethylformamide (3 L, dried over 4-Å molecular sieves) and the mixture was stirred overnight at room temperature. Most of the solvent was removed in vacuo and the residue partitioned between water and diethyl ether. The organic phase was washed with 2% tartaric acid and then saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and evaporated. The residue (783 g) was filtered over 1.5 kg of silica gel (toluene/ethyl acetate = 4/1), and after evaporation, a viscous oil (633.4 g, 72.4%) was obtained. HPLC analysis showed 74.5% **4a** and 25.4% **8a**. After dissolving in ethanol, an equimolar amount of ethanolic HCl- solution was added and evaporated to dryness. The crystalline residue was dissolved in hot 2-propanol (1.2 L) and diethyl ether added (4 L). After some hours the crystals were filtered by suction and washed with 2-propanol/diethyl ether (1/1). Recrystallization from 2-propanol/diethyl ether gave the analytically pure hydrochloride of the trans isomer **4a** (427.9 g, 43.5%) as colorless crystals: mp 195–198 °C (change in crystal structure beginning from about 150 °C); NMR (base) δ 8.2–8.35 (m, 1 H), 7.7–7.9 (m, 2 H), 7.3–7.6 (m, 4 H), 6.18 (dt, *J* = 15 and 2 × 6.5 Hz, (*E*)-CH_2CH=CH), 5.67 (dt, *J* = 15 and 2 × 1.5 Hz, (*E*)-CH_2CH=CH), 3.9 (s, Ar CH_2N), 3.13 (dd, *J* = 6.5 and 1.5 Hz, NCH_2CH=), 2.22 (s, NCH_3), 1.25 (s, *t*-Bu). Anal. ($C_{21}H_{25}N$·HCl) C, H, N, Cl.

Compound **8a** was obtained by chromatography of the crude reaction mixture (toluene/ethyl acetate = 9/1). After elution of trans isomer **4a** (TLC, R_f 0.36) pure cis isomer **8a** (TLC, R_f 0.28, oil) was isolated: NMR identical with **4a**, except for δ 6.02 (dt, *J* = 10 and 2 × 6.5 Hz, (*Z*)-CH_2CH=CH), 5.66 (dt, *J* = 10 and 2 × 1.5 Hz, (*Z*)-CH=CHC≡), 3.38 (dd, *J* = 6.5 and 1.5 Hz, NCH_2CH=); MS, *m/e* 291.

Compound **4b** and its *Z* isomer **8b** were prepared as described for **4a** and **8a**, starting from **7b** (7.2 g, 35.8 mmol). Chromatography (toluene/ethyl acetate = 9/1) of the crude reaction product yielded pure **4b** (5.61 g, 53.8%, oil) and **8b** (1.36 g, 13%, oil). **8b**: NMR identical with **4b**, except for δ 6.05 (dt, *J* = 10 and 2 × 6.5 Hz, (*Z*)-CH_2CH=CH), 5.65 (dd, *J* = 10 and 2 × 1.5 Hz, (*Z*)-CH=CHC≡), 3.38 (dd, *J* = 6.5 and 1.5 Hz, NCH_2CH=); MS, *m/e* 291.

(*E*)-*N*-Methyl-*N*-(6-methyl-2-octen-4-ynyl)-1-naphthalenemethanamine (4c) and its *Z* isomer 8c were prepared as described for **4a** and **8a**, starting from **7c** (6.48 g, 32.2 mmol). Chromatography (toluene/ethyl acetate = 95/5) of the crude reaction product yielded pure **4c** (4.23 g, 45%, oil) and **8c** (0.94 g, 10%, oil).

Compound **4**: mp (hydrochloride) 160–162 °C; NMR (base) δ 6.20 (dt, *J* = 15 and 2 × 6.5 Hz, (*E*)-CH_2CH=CH), 5.80 (dt, *J* = 15 and 2 × 1.5 Hz, (*E*)-CH=CHC≡), 3.9 (s, Ar CH_2N), 3.14 (dd, *J* = 6.5 and 1.5 Hz, NCH_2CH=), 2.5 (m, =C*CH*), 2.24 (s, NCH_3), 1.2–1.7 (m, 2 H), 1.18 (d, *J* = 7 Hz, Me), 1.0 (t, *J* = 7 Hz,

Me). Anal. ($C_{21}H_{25}N$·HCl) C, H, N, Cl.

Compound **8c**: NMR identical with **2c** except for δ 6.05 (dt, J = 10 and 2 × 6.5 Hz, (Z)-CH_2CH=CH), 5.67 (dt, J = 10 and 2 × 1.5 Hz, (Z)-CH=CHC≡), 3.4 (dd, J = 6.5 and 1.5 Hz, NCH_2CH=); MS, m/e 291.

(*E*,*E*)-*N*-Methyl-*N*-2,4-nonadienyl-1-naphthalenemethanamine (2). A solution of (*E*,*E*)-2,4-nonadienal (20 g, 127 mmol) and 1-naphthalenemethanamine (20.4 g, 127 mmol) in benzene was boiled in a Dean–Stark apparatus until the calculated amount of water had separated. After removal of solvent, the Schiff base was taken up in methanol, treated with solid $NaBH_4$ (4,8 g, 127 mmol) in several portions at 40 °C, and stirred for 1 h at this temperature. This reaction mixture was used directly for reductive methylation[17] following the procedure of Sondengam.[18] Aqueous 35% formaldehyde solution (57 mL, 636 mmol) was added and the reaction mixture refluxed for 1 h. The mixture was then treated under ice cooling with solid $NaBH_4$ (24 g, 636 mmol) in several portions and stirred at room temperature overnight. After concentration, the residue was partitioned between aqueous $NaHCO_3$ solution and ethyl acetate and the organic phase dried and concentrated. The crude **7** (37.2 g, quant) thus obtained was shown by TLC and NMR to be of about 80% purity. Chromatography (toluene/ethyl acetate = 9/1) over silica furnished pure **2** (25 g, 67%) as a colorless oil: NMR for NCH_2-(*E*)-CH_α=CH_β-(*E*)-CH_γ=$CH_\delta CH_2$, 6.18 (H_β), 6.08 (H_γ), 5.72 (H_α), 5.65 (H_δ); $J_{H_\alpha CH_2N}$ = 6.75 Hz, $J_{H_\alpha H_\beta}$ = 14.5 Hz, $J_{H_\delta CH_2N}$ = 1.2 Hz, $J_{H_\beta H_\gamma}$ = 10.3 Hz, $J_{H_\gamma H_\delta}$ = 14.5 Hz, $J_{H_\gamma CH_2}$ = 1.35 Hz, $J_{H_\delta CH_2}$ = 6.9 Hz; 3.87 (s, Ar CH_2N), 3.13 (dd, NCH_2CH=), 1.9–2.2 (m, =CCH_2). Anal. ($C_{21}H_{27}N$) C, H, N.

(*E*)-*N*-Methyl-*N*-4-nonen-2-ynyl-1-naphthalenemethanamine (9a) and Its *Z* Isomer 9b. 3-Octen-1-yne[19] (3.2 g, 15.8 mmol, *E*/*Z* = 1:2), *N*-methyl-1-naphthalenemethanamine (2.7 g, 15.8 mmol), paraformaldehyde (0.47 g, 15.8 mmol), and CuCl (0.16 g, 1.58 mmol) were reacted as described for the preparation of **3a** by Mannich condensation. By chromatography (hexane/butyl acetate = 10/1) of the crude reaction mixture the stereoisomers could be separated. Z isomer **9b** (1.58 g, 34%, DC R_f 0.46, oil) was isolated first, followed by a 1:1 mixture of **9a** and **9b** (1.72 g, 37%) and a pure sample of **9a** (0.19 g, 4%, DC R_f 0.42, oil).

Compound **9a**: NMR δ 6.22 (dt, J = 16 and 2 × 7 Hz, (*E*)-CH=$CHCH_2$), 5.58 (dm, J = 16 Hz, ≡C-(*E*)-CH=CH), 4.0 (s, Ar CH_2N), 3.44 (d, J = 1.5 Hz, NCH_2C≡), 2.38 (s, NCH_3), 2.0–2.3 (m, =CCH_2); mp (hydrochloride) 103–106 °C. Anal. ($C_{21}H_{25}N$·HCl) C, H, N, Cl.

Compound **9b**: NMR identical with **8a** except for δ 5.95 (dt, J = 11 and 7 Hz, (*Z*)-CH=$CHCH_2$), 5.55 (dm, J = 11 Hz, ≡C-(*Z*)-CH=CH), 3.49 (d, J = 1.5 Hz, NCH_2C≡), 2.2–2.5 (m, =CCH_2).

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Registry No. **2**, 92525-78-5; **3a**, 92525-79-6; **3a**·HCl, 92525-80-9; **3b**, 78628-65-6; **4a**, 91161-71-6; **4b**, 78628-64-5; **4b**·HCl, 78628-66-7; **4c**, 92525-81-0; **5a**, 92525-82-1; **5b**, 92525-83-2; **6a**, 78629-20-6; **6b**, 67978-48-7; **6c**, 78629-22-8; (*E*)-**7a**, 78629-21-7; (*Z*)-**7a**, 78629-19-3; (*E*)-**7b**, 67978-51-2; (*Z*)-**7b**, 67978-52-3; (*E*)-**7c**, 78629-28-4; (*Z*)-**7c**, 78629-29-5; **8a**, 78628-81-6; **8b**, 78628-73-6; **8c**, 78628-85-0; **9a**, 92525-84-3; **9b**, 92525-85-4; R_1NHCH_3, 14489-75-9; $R_1N(CH_3)$-CH_2C≡CH, 2321-99-5; R_1NH_2, 118-31-0; *t*-BuC≡CC≡CH, 4911-56-2; *n*-BuC≡CBr, 1119-64-8; *t*-BuC≡CH, 917-92-0; CH_2=CHCHO, 107-02-8; *n*-BuC≡CH, 693-02-7; *sec*-BuC≡CH, 922-59-8; (*E*,*E*)-*n*-BuCH=CHCH=CHCHO, 5910-87-2; (*E*)-*n*-BuCH=CHC≡CH, 42104-42-7; (*Z*)-*n*-BuCH=CHC≡CH, 42091-89-4.

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Pyridonecarboxylic Acids as Antibacterial Agents. 4.[1] Synthesis and Antibacterial Activity of 7-(3-Amino-1-pyrrolidinyl)-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid and Its Analogues

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The title compounds (**28–56**) with an amino- and/or hydroxy-substituted cyclic amino group at C-7 were prepared with 1-substituted 7-chloro-, 7-(ethylsulfonyl)-, and 7-(tosyloxy)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acids and their ethyl esters (**3–7**) with cyclic amines such as 3-aminopyrrolidine. The N-1 substituent includes ethyl, vinyl, and 2-fluoroethyl groups. As a result of in vitro and in vivo antibacterial screenings, three compounds, 1-ethyl- and 1-vinyl-7-(3-amino-1-pyrrolidinyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acids (**33a** and **33b**) and 1-vinyl-7-[3-(methylamino)-1-pyrrolidinyl] analogue **34b**, were found to be more active than enoxacin (**2**) and to be worthy of further biological study. Structure–activity relationships are discussed.

As exemplified by pipemidic acid (**1**),[2] we showed first that a piperazinyl group was of much importance for the improvement of antibacterial activity and pharmacokinetic properties of a class of pyridonecarboxylic acid antibacterial agents. During the last few years, several analogues having both fluoro and piperazinyl groups in their molecules were reported successively;[3,4] their antibacterial activities are noticeably much more potent and broader than

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