Synthetic Acetylenic Antifungal Agents

D. Z. SIMON, S. BROOKMAN [x], J. BELIVEAU, and R. L. SALVADOR

Abstract □ Several monoamino bis(propynyloxy)benzenes were prepared by a Mannich reaction and tested for antifungal activity against *Trichophyton schoenleini, T. mentagrophytes, T. tonsurans, Candida albicans,* and *Epidermophyton flocossum.* In addition, the bis(propynyloxy)benzene intermediates were tested and comparisons were made with standard drugs. The intermediates were found to be the most active, although two Mannich bases possessed considerable activity.

Keyphrases □ Bis(propynyloxy)benzenes and monoamino derivatives—synthesized, screened for antifungal activity □ Antifungal activity—screened in various bis(propynyloxy)benzenes and monoamino derivatives □ Structure–activity relationships—various bis(propynyloxy)benzenes and monoamine derivatives screened for antifungal activity

The isolation of 1-oxo-1-phenylhexa-2,4-diyne from the essential oil of *Artemisia capillaris* Thunb. (Compositae) (1) and the subsequent isolation and synthesis of acetylenecarboxamide (2, 3) have led many investigators to synthesize related acetylenic compounds and to examine their antifungal properties (4). Some mercury acetylides (5), amino polyenes (6), and monoamino alkynes (7) were prepared that were effective antifungal agents. In addition, acetylenic amino esters and diamines with antifungal action were synthesized (8).

Among a large series of compounds (9–13), 3-iodopropargyl ethers exhibited considerable antifungal activity when they possessed an aryl group that was either phenyl or naphthyl substituted by at least one electronegative group. This finding led to the clinically successful agent haloprogin, 1,2,4-trichloro-5-[(3-iodo-2-propynyl)-oxy]benzene (14). A new series of phenyl ethers, which might prove interesting from this aspect, was synthesized (Scheme I).

RESULTS AND DISCUSSION

Bis(propynyloxy)benzenes (I) were prepared *via* a Williamson synthesis, as previously described (15). Under Mannich reaction conditions with formaldehyde solution and various dialkylamines, a series of monoamino bis(propynyloxy)benzenes (II) was obtained; confirmation was by elemental analysis and IR and NMR spectroscopy (Table I). Attempts at synthesizing the *o*-dimethylamino and *o*-diethylamino Mannich bases failed, probably due to steric hindrance.

The antifungal activity of all compounds, *i.e.*, types I and II, was determined *in vitro* [1] against *Trichophyton schoenleini, T. mentagrophytes, T. tonsurans, Candida albicans,* and *Epidermophyton flocossum.* All compounds were dissolved in dimethyl sulfoxide at a concentration of 5 μg/ml. The antifungal properties of the active substances are reported in Table II and were compared to haloprogin and griseofulvin.

Antifungal activity was observed with I*a*, I*b*, and I*c*. The Mannich bases II*a* and II*d* showed some activity, although the remaining bases did not. In addition, considerable growth inhibition was visible by II*a* against *E. flocossum.* Therefore, it appeared that the introduction of an alkylamino group onto one propargyl chain led to diminished antifungal properties.

[1] A cylinder plate method on a Sabouraud dextrose agar medium (Difco), pH 5.9, was used. The plates were subjected to preincubation (period of diffusion) at 4° for 1 hr and then incubated at 25° for 72 hr. The zones of inhibition were measured, each value representing the average of three trials. Control agar plates using dimethyl sulfoxide were included in each trial series. The microorganisms were obtained from the fungi collection of the Department of Microbiology, University of Montreal, Montreal 101, Canada.

EXPERIMENTAL [2]

1,2-Bis(2-propynyloxy)benzene (I*a*)—To 75 ml of acetone, 11 g (0.1 mole) of catechol, 27.6 g (0.2 mole) of anhydrous potassium carbonate, and 23.8 g (0.2 mole) of propargyl bromide were added, and the mixture was refluxed under nitrogen for 8 hr. The mixture was filtered, and the resulting filtrate was evaporated under reduced pressure. The residue was dissolved in ether, washed with 10% sodium hydroxide and water, and dried over anhydrous potassium carbonate. The solvent was evaporated under reduced pressure, and the resulting oil was heated in *n*-pentane. Decanting and evaporating the supernate yielded 13.1 g (70%) of I*a*, mp 30.5–31°; IR (ν_{max}): 3285 (acetylenic CH) and 2115 (monosubstituted C≡C) cm^{-1}; NMR: 2.4 (t, 2H, J = 2.6 Hz), 4.65 (d, 4H, J = 2.6 Hz), and 6.95 (s, 4H) ppm; TLC: R_f 0.50 (chloroform).

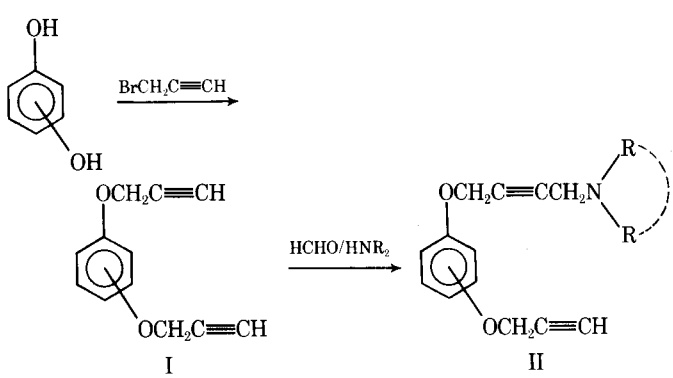
1,3-Bis(2-propynyloxy)benzene (I*b*)—Compound I*b* was prepared from resorcinol as described for I*a*, yielding 15.8 g (85%), mp 37.5–38°; NMR: 2.6 (t, 2H, J = 2.6 Hz), 4.7 (d, 4H, J = 2.6 Hz), 6.6 (m, 3H), and 7.2 (t, 1H, J = 8.0 Hz) ppm; TLC: R_f 0.8 (chloroform).

1,4-Bis(2-propynyloxy)benzene (I*c*)—Compound I*c* was prepared from hydroquinone as described for I*a*, yielding 16.8 g (87%), mp 49.5–50°; NMR: 2.6 (t, 2H, J = 2.6 Hz), 4.8 (d, 4H, J = 2.6 Hz), and 7.2 (s, 4H) ppm; TLC: R_f 0.55 [chloroform–carbon tetrachloride (7:3)].

1-(4-Dimethylamino-2-butynyloxy)-4-(2-propynyloxy)benzene (II*a*)—To 35 ml of dioxane, 16.2 ml (0.216 mole) of 40% formaldehyde and 10 g (0.054 mole) of I*c* were added, and the solution was placed in a 250-ml pressure flask. Dimethylamine, 19.4 g (0.432 mole), was added, and the flask was sealed and heated at 80° for 140 hr. The reaction flask was cooled prior to opening. The solvents were evaporated under reduced pressure; the residue was dissolved in ether and washed with several portions of 10% sodium bisulfite and then water until neutral washings resulted. The organic phase was extracted with 250 ml of 10% HCl, the aqueous fraction was made alkaline with a slurry of sodium bicarbonate, and the free base was extracted with ether and dried over anhydrous potassium carbonate. The solvent was removed to yield 4.02 g (31%) of II*a*, mp 34–35°; IR (ν_{max}): 3290 (acetylenic CH) and 2110 (monosubstituted C≡C) cm^{-1}; NMR: 2.15 (s, 6H), 2.4 (t, 1H, J = 2.6 Hz), 3.2 (d, 2H, J = 2.0 Hz), 4.6 (m, 4H), and 6.9 (s, 4H) ppm.

Mannich Bases—The following Mannich bases were prepared similarly.

1-(4-Diethylamino-2-butynyloxy)-4-(2-propynyloxy)benzene (II*b*)—NMR: 1.0 (t, 6H, J = 6.3 Hz), 2.4 (m, 5H), 3.35 (t, 2H, J = 2.0 Hz), 4.6 (m, 4H), and 6.85 (s, 4H) ppm.



Scheme I

[2] Melting points were measured by the capillary method on a Buchi melting-point apparatus and are uncorrected. Carbon, hydrogen, and nitrogen were determined by Dr. C. Daessle, Montreal, Canada. Amine bases were analyzed in the form of their picrate salts, and the results obtained are within 0.4% of the theoretical values. IR spectra were recorded on a Beckman IR 18A spectrophotometer. NMR spectra were recorded on a Perkin-Elmer R 12B spectrometer in carbon tetrachloride. The tetramethylsilane signal was taken as the internal reference. The proton signals are designated by the following abbreviations: s, singlet; d, doublet; t, triplet; and m, multiplet. TLC plates, 0.5 mm thick, were prepared using silica gel G, and the compounds were detected with iodine vapors.

Table I—Physical Constants of Monoamino Bis(propynyloxy)benzenes

Compound	Yield, %	Melting Point	Boiling Point	Formula (Picrate)	Analysis, % Calc.	Found
II*a*	31	34–35°	—	$C_{21}H_{20}N_4O_9$	C 53.39	53.16
					H 4.24	4.47
					N 11.86	11.68
II*b*	38	20–21°	—	$C_{23}H_{24}N_4O_9$	C 55.20	54.92
					H 4.80	5.07
					N 11.20	10.96
II*c*	31	44–46°	—	$C_{23}H_{22}N_4O_{10}$	C 53.70	53.46
					H 4.28	4.14
					N 10.89	11.10
II*d*	22	49–51°	—	$C_{23}H_{22}N_4O_{10}$	C 53.70	53.48
					H 4.28	4.27
					N 10.89	11.14
II*e*	12	—	118°/ 0.005 mm	$C_{21}H_{20}N_4O_9$	C 53.39	53.43
					H 4.24	4.44
					N 11.86	12.13
II*f*	13	—	130–132°/ 0.005 mm	$C_{23}H_{24}N_4O_9$	C 55.20	55.13
					H 4.80	5.05
					N 11.20	11.31
II*g*	30	152–153° (picrate)	—	$C_{23}H_{22}N_4O_{10}$	C 53.70	53.96
					H 4.28	4.44
					N 10.89	11.05

Table II—Antifungal Activity of Bis(propynyloxy)benzenes and Their Mannich Bases[a]

Compound	*T. schoenleini*	*T. tonsurans*	*T. mentagrophytes*	*E. flocossum*	*C. albicans*
Control	–	–	–	–	–
I*a*	+	+	+	2+	+
I*b*	+	2+	2+	2+	2+
I*c*	+	2+	2+	2+	2+
II*a*	+	+	+	+	+
II*d*	+	+	+	2+	+
Griseofulvin	+	+	+	2+	–
Haloprogin	+	2+	3+	3+	2+

[a] Inhibition zones expressed as follows: –, inhibition; +, 10–25 mm; 2+, 26–40 mm; and 3+, 41–55 mm.

1-(4-Morpholino-2-butynyloxy)-4-(2-propynyloxy)benzene (II*c*) —NMR: 2.5 (m, 5H), 3.3 (t, 2H, J = 2.0 Hz), 3.7 (m, 4H), 4.7 (t, 4H, J = 5.3 Hz), and 6.9 (s, 4H) ppm.

1-(4-Morpholino-2-butynyloxy)-2-(2-propynyloxy)benzene (II*d*) —NMR: 2.5 (m, 5H), 3.35 (t, 2H, J = 2.0 Hz), 3.7 (t, 4H, J = 5.3 Hz), 4.8 (m, 4H), and 7.0 (s, 4H) ppm.

1-(4-Dimethylamino-2-butynyloxy)-3-(2-propynyloxy)benzene (II*e*)—NMR: 2.2 (s, 6H), 2.4 (t, 1H, J = 2.6 Hz), 3.25 (t, 2H, J = 2.0 Hz), 4.6 (m, 4H), and 6.5–7.2 (m, 4H) ppm.

1-(4-Diethylamino-2-butynyloxy)-3-(2-propynyloxy)benzene (II*f*)—NMR: 1.1 (t, 6H, J = 6.3 Hz), 2.5 (m, 5H), 3.45 (t, 2H, J = 2.0 Hz), 4.7 (m, 4H), and 6.6–7.3 (m, 4H) ppm.

1-(4-Morpholino-2-butynyloxy)-3-(2-propynyloxy)benzene (II*g*) —NMR: 2.5 (m, 5H), 3.4 (t, 2H, J = 2.0 Hz), 3.7 (t, 4H, J = 5.3 Hz), 4.8 (m, 4H), and 6.8–7.4 (m, 4H) ppm.

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[x] To whom inquiries should be directed. Present address: Institut de médecine et de chirurgie expérimentales, Université de Montreal, Montreal 101, Quebec, Canada.