

2-Phenylpyrazolo[1,5-*a*]pyrimidin-7-ones. A New Class of Nonsteroidal Antiinflammatory Drugs Devoid of Ulcerogenic Activity

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Syntheses of some pyrazolo[1,5-*a*]pyrimidines were performed in order to study the relationship between structural modifications on the parent 4,7-dihydro-2-phenylpyrazolo[1,5-*a*]pyrimidin-7-one (1) and their antiinflammatory properties. The modifications carried out were introduction and functionalization of a longer side chain at the 4-position, substitution of the hydrogen atom at the 3-position, and replacement of the phenyl group with a 4-methylphenyl, methyl, or hydrogen substituent. 4-Ethyl-4,7-dihydro-2-phenylpyrazolo[1,5-*a*]pyrimidin-7-one (3) showed the highest activity and a better therapeutic index than phenylbutazone and indomethacin, used as reference drugs. All other changes at the 3-, 5-, and 6-positions, as well as the replacement of the phenyl group at position 2, caused a marked decrease of activity. Compound 3 was found devoid of ulcerogenic activity and was probably endowed with antiulcerogenic properties.

Gastric ulceration and hemorrhage are the major problems in therapy with antiinflammatory drugs. These side effects become evident mainly during chronic therapy with NSAID compounds. The ulcerogenic activity shown by all antiinflammatory drugs presently used is probably due to inhibition of prostaglandin biosynthesis at the gastric mucosal level.¹ It is also possible that the erosive properties of acidic groups frequently present in these compounds could enhance this gastrototoxic effect.² Following these considerations, we thought it of interest to study the pharmacological properties of new compounds devoid of acidic functions in order to verify whether it was possible to dissociate the antiinflammatory activity and the properties of NSAID drugs to induce gastric mucosal damage and ulceration.

Previous papers³ reported the syntheses of several 2-phenylpyrazolo[1,5-*a*]pyrimidines and the interesting antipyretic and antiinflammatory activity of 4,7-dihydro-4-methyl-2-phenylpyrazolo[1,5-*a*]pyrimidin-7-one (2). A study of the pharmacological properties and structure-activity relationships in the pyrazolo[1,5-*a*]pyrimidine series required the preparation of new derivatives of the parent structure 1.

Modifications at the 4-position were carried out to study how the antiinflammatory activity varied when a longer or a functionalized side chain was introduced. In addition, some 3-substituted derivatives of 1 and pyrazolo[1,5-*a*]pyrimidines bearing at the 2-position substituents such as hydrogen, methyl, and 4-methylphenyl were prepared and tested. The latter ones were useful to indicate the fundamental role played by the phenyl moiety. Furthermore, some alkyl derivatives of 4,5-dihydro-2-phenylpyrazolo[1,5-*a*]pyrimidin-5-one (25) were prepared in order to compare their activity with that of the respective derivatives of 1.

We discovered that 4-ethyl-4,7-dihydro-2-phenylpyrazolo[1,5-*a*]pyrimidin-7-one (3) is a drug with a powerful antiinflammatory and analgesic activity devoid, in our tests, of ulcerogenic action and probably having antiulcer properties. The pyrazolo[1,5-*a*]pyrimidines studied are listed in Table I.

Chemistry. Compounds 1, 13, 15, and 17 were prepared by reacting a suitable 3(5)-aminopyrazole with sodium formylacetate, according to a known method.^{3b} Alkylations were carried out with dialkyl sulfates (footnote *b*, Table I) or with alkyl halides (footnote *c*, Table I) in accordance with reported procedures.⁴

Reaction of 25 with ethyl and propyl iodide gave 26 and 27, respectively, in mixture with 28 and 29. Separation of the isomers was performed by preparative TLC, and their IR and NMR spectra are in accordance with known structures.

Compound 24 was obtained by reacting 1 with NaNO₂ in HCl/CH₃COOH and treating the nitroso intermediate 23 with C₂H₅I at room temperature.

Compound 3 reacted with Br₂ or *N*-bromosuccinimide in CCl₄ to yield a mixture of the dibromo derivative 19 and the bromo derivative 20, which were separated by preparative TLC.

Thiocyanation of 3, performed in accordance with a recent method,⁵ afforded 21, whose alkaline hydrolysis⁶ gave the disulfide 22. The structure of the latter was verified by mass spectroscopy.

Pharmacology. The antiinflammatory and antiarthritic activities of the compounds are shown in Table II. Compounds 2-4, belonging to general formula A with the alkyl group in position 4, displayed the best antiinflammatory properties. A second alkyl group in position 5 or 6 decreased this activity, which became minimal in compound 11.

A change of the carbonyl function from position 7 to position 5 (26, 27) eliminates the antiinflammatory properties, suggesting no steric bulk can be allowed in position 5 or 6 to retain significant pharmacological activity. A reduction of activity was also observed when the phenyl group at the 2-position was replaced by other substituents (14, 16, and 18), as well as when substitutions were performed at position 3 (19-22 and 24).

A more thorough investigation was carried out in order to verify the course of the antiinflammatory and analgesic activity with elongation of the alkyl chain at position 4. The 4-ethyl-substituted 3 possesses the minimal ED₅₀. A further increase of the carbon chain (4 and 6) decreased the pharmacological properties, probably by steric hin-

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Table I. Physical Properties of Substituted Pyrazolo[1,5-a]pyrimidines

compd	R	R ₁	R ₂	R ₃	R ₄	mp, °C	recrystn solvent	yield, %	formula
<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;"> <p>A</p> </div> <div style="text-align: center;"> <p>B</p> <p>25-27</p> </div> <div style="text-align: center;"> <p>C</p> <p>28-29</p> </div> </div>									
1 ^a	C ₆ H ₅	H	H	H	H	330	EtOH	40	C ₁₂ H ₉ N ₃ O
2 ^a	C ₆ H ₅	H	CH ₃ ^b	H	H	214-217	H ₂ O	70	C ₁₃ H ₁₁ N ₃ O
3	C ₆ H ₅	H	C ₂ H ₅ ^{b,c}	H	H	151-153	EtOAc	30	C ₁₄ H ₁₃ N ₃ O
4	C ₆ H ₅	H	<i>n</i> -C ₃ H ₇ ^c	H	H	127-129	H ₂ O	20	C ₁₅ H ₁₅ N ₃ O
5	C ₆ H ₅	H	<i>i</i> -C ₃ H ₇ ^c	H	H	141-143	MeOH/H ₂ O	22	C ₁₅ H ₁₅ N ₃ O
6	C ₆ H ₅	H	<i>n</i> -C ₄ H ₉ ^c	H	H	128-130	EtOAc	30	C ₁₆ H ₁₇ N ₃ O
7	C ₆ H ₅	H	C ₂ H ₅ -CH ₂ ^c	H	H	165-166	EtOAc	40	C ₁₉ H ₁₅ N ₃ O
8	C ₆ H ₅	H	CH ₂ CH(OC ₂ H ₅) ₂ ^c	H	H	100-103	H ₂ O	24	C ₁₈ H ₂₁ N ₃ O ₃
9	C ₆ H ₅	H	CH ₂ CH ₂ OH ^c	H	H	203-205	EtOH	18	C ₁₄ H ₁₃ N ₃ O ₂
10	C ₆ H ₅	H	CH=CHCOOC ₂ H ₅	H	H	200-202	EtOH	30	C ₁₇ H ₁₅ N ₃ O ₃
11 ^d	C ₆ H ₅	H	CH ₃	CH ₃	H	233-235	H ₂ O	60	C ₁₄ H ₁₃ N ₃ O
12 ^d	C ₆ H ₅	H	CH ₃	H	CH ₃	192-194	EtOH/H ₂ O	45	C ₁₄ H ₁₃ N ₃ O
13	4-CH ₃ C ₆ H ₄	H	H	H	H	>300	DMF	40	C ₁₃ H ₁₁ N ₃ O
14	4-CH ₃ C ₆ H ₄	H	C ₂ H ₅ ^b	H	H	210	EtOH	35	C ₁₅ H ₁₅ N ₃ O
15	CH ₃	H	H	H	H	275-278	C ₆ H ₆	30	C ₈ H ₇ N ₃ O
16	CH ₃	H	C ₂ H ₅ ^b	H	H	150-152	cyclohexane/acetone	23	C ₉ H ₁₁ N ₃ O
17	H	H	H	H	H	335-337	EtOH/H ₂ O	15	C ₈ H ₅ N ₃ O
18	H	H	CH ₃ ^b	H	H	200-201	EtOAc	20	C ₈ H ₇ N ₃ O
19	C ₆ H ₅	Br	C ₂ H ₅	H	Br	190-193	EtOH	5	C ₁₄ H ₁₁ BrN ₃ O
20	C ₆ H ₅	Br	C ₂ H ₅	H	H	175-177	H ₂ O	7	C ₁₄ H ₁₂ BrN ₃ O
21	C ₆ H ₅	SCN	C ₂ H ₅	H	H	173-174	MeOH	60	C ₁₅ H ₁₂ N ₄ OS
22	C ₆ H ₅	S ₂	C ₂ H ₅	H	H	>300	HOAc	65	C ₂₈ H ₂₄ N ₆ O ₂ S ₂
23	C ₆ H ₅	NO	H	H	H	240-242	EtOH	25	C ₁₂ H ₈ N ₄ O ₂
24	C ₆ H ₅	NO	C ₂ H ₅ ^c	H	H	183-185	EtOAc	15	C ₁₄ H ₁₂ N ₄ O ₂
25 ^a	C ₆ H ₅	H	H	H	H	284-286	EtOH	20	C ₁₂ H ₉ N ₃ O
26	C ₆ H ₅	H	C ₂ H ₅ ^{b,c}	H	H	142-143	EtOH/H ₂ O	5	C ₁₄ H ₁₃ N ₃ O
27	C ₆ H ₅	H	<i>n</i> -C ₃ H ₇ ^c	H	H	97-99	MeOH	7	C ₁₅ H ₁₅ N ₃ O
28	C ₆ H ₅	H	C ₂ H ₅ ^c	H	H	124-125	H ₂ O	5	C ₁₄ H ₁₃ N ₃ O
29	C ₆ H ₅	H	<i>n</i> -C ₃ H ₇ ^c	H	H	118-120	EtOH	7	C ₁₅ H ₁₅ N ₃ O

^a Reference 3b. ^b Alkylation with dialkyl sulfate. ^c Alkylation with alkyl halide. ^d Reference 4a.

drance (Tables III and IV). These results agreed with those obtained when compounds bearing substitutions other than a normal alkyl group in the 4-position were tested for antiinflammatory activity (Table II) (5 and 7-10).

The aim of our work was also to investigate the toxicological properties of some of the more active compounds. The LD₅₀ and the ulcerogenic properties of these substances are shown in Table V, compared with those of phenylbutazone and indomethacin. Compounds 2 and 3 were devoid of ulcerogenic activity, while the reference drugs, in the same test, showed a strong gastrototoxicity. When 3 was administered in association with phenylbutazone, a significant reduction of ulceration was observed in restrain stressed rats, compared with phenylbutazone-treated animals (Figure 1). Moreover, the antiinflammatory activity of phenylbutazone (10 mg/kg) in combination with compound 3 (100 mg/kg) was higher than that of phenylbutazone alone (73 and 34%, reduction of edema, respectively).

Compound 3, in preliminary experiments, showed a weak inhibitory activity of guinea pig lung prostaglandin biosynthesis, and this could explain the apparent lack of gastrototoxicity of this nonacidic compound. On the contrary, it is impossible at the moment to explain the observed antiulcer properties of this compound. Activity on the central or peripheral nervous system, as well as modifications of gastric secretions, may play a role in this effect.

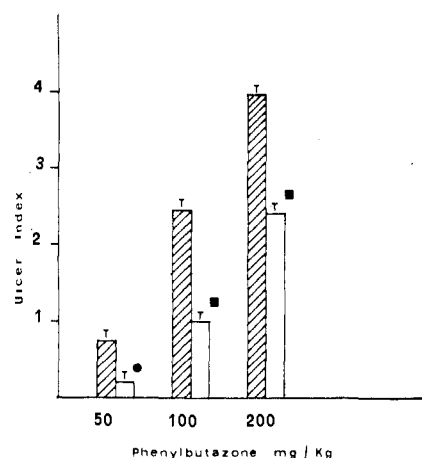


Figure 1. Antiulcer effect of compound 3 in phenylbutazone-treated rats. Student's *t* test: (●) >0.01; (■) >0.005. Nonhatched bars are phenylbutazone plus compound 3 (150 mg/kg).

These properties, together with good antiinflammatory and analgesic activities of 4-ethyl-4,7-dihydro-2-phenylpyrazolo[1,5-a]pyrimidin-7-one (3), led us to extend our investigations in view of a possible therapeutical interest in this compound.

Experimental Section

Melting points were determined on a Büchi 510 melting point apparatus and are uncorrected. Elemental analyses were per-

Table II. Antiinflammatory and Antiarthritis Assay

compd	dose, mg/kg, po	carrageenin model, % reduction of edema, 3 h	arthritis assay, 23rd day, % reduction of edema ^a
1	300	27.3 ± 7.8	<i>i</i>
2	30	54.0 ± 6.8	29.8 ± 9.9
3	17	54.1 ± 6.6	
	30		42.7 ± 13.9
4	30	52.1 ± 11.1	33.0 ± 17.2
5	20	3.5 ± 3.5	<i>i</i>
6	20	26.6 ± 9.9	59.8 ± 16.4
7	20	5.8 ± 3.2	18.2 ± 7.7
8	20	12.5 ± 5.3	<i>i</i>
9	30	16.5 ± 2.8	<i>i</i>
10	30	23.4 ± 6.9	<i>i</i>
11	50	56.7 ± 8.3	<i>i</i>
12	300	68.7 ± 5.3	<i>i</i>
14	30	35.9 ± 7.6	<i>i</i>
16	30	7.3 ± 3.07	<i>i</i>
18	20	0	<i>i</i>
19	30	0	<i>i</i>
20	30	40.5 ± 13.0	<i>i</i>
21	30	42.2 ± 4.9	<i>i</i>
22	30	37.5 ± 10.1	<i>i</i>
24	30	7.03 ± 6.2	<i>i</i>
26	100	32.2 ± 8.5	25.7 ± 17.5
27	30	18.9 ± 7.8	<i>i</i>
indomethacin	3	62.4 ± 4.8	39.0 ± 14.0
phenylbutazone	20	52.9 ± 3.9	20.7 ± 2.4

^a *i* = inactive.Table III. Antiinflammatory Activity of *N*-Alkyl-Substituted Compounds. Carrageenin Model

compd	dose, mg/kg, po	% reduction of edema, 3 h	ED ₅₀ ^a , mg/kg
2	10	34.2 ± 8.2	
	25	55.1 ± 7.3	24.7 (7.2-84.6)
	100	67.5 ± 7.9	
3	10	54.1 ± 4.9	
	25	69.8 ± 4.1	7.3 (2.4-22.1)
	100	90.1 ± 2.6	
4	20	31.9 ± 9.8	
	30	52.1 ± 11.1	29.8 (16.6-52.9)
	50	70.8 ± 7.8	
indomethacin	1	36.7 ± 5.9	
	3	62.4 ± 4.8	1.83 (0.56-5.9)
	5	69.2 ± 6.8	
phenylbutazone	10	48.7 ± 3.1	
	25	52.9 ± 3.9	13.1 (3.2-53.9)
	50	62.9 ± 3.8	

^a 95% confidence limits in parentheses.Table IV. Analgesic Activity of *N*-Alkyl-Substituted Compounds 2 and 3. Acetic Acid Writhing Test

compd	dose, mg/kg, po	% analgesic effect	ED ₅₀ ^a , mg/kg
2	60	43.0	
	80	53.3	69.6 (51.7-96.4)
	120	80.7	
3	5	24.5	
	15	69.3	9.86 (5.9-16.5)
	30	84.3	
	0.3	20.0	
indomethacin	1.0	28.0	2.5 (0.8-7.3)
	3.0	57.0	
	120	28.4	
phenylbutazone	300	57.7	273.6 (173.3-411)
	500	73.0	

^a 95% confidence limits in parentheses.

formed for C, H, and N, with a Perkin-Elmer 260 C elemental analyzer, and results were within ±0.4% of the theoretical values.

IR spectra were taken routinely in Nujol mulls with a Perkin-Elmer 337 spectrophotometer and with a Perkin-Elmer 983 instrument when required. ¹H NMR spectra were recorded with a Varian EM 360 instrument (chemical shifts are reported in δ, parts per million, downfield from internal tetramethylsilane). Mass spectra were run on a LKB 2091 mass spectrometer operating at an electron energy of 70 eV and a 3.5-kV accelerating voltage with a direct-inlet system at 300 °C. Silica gel plates (Merck F₂₅₄) were used for analytical and preparative chromatography.

Alkylation of Pyrazolo[1,5-*a*]pyrimidines. With Dialkyl Sulfate (3, 14, 16, 18, and 26). To compound 1, 13, 15, 17, or 25 (0.02 mol) dissolved in the least amount of hot 1 N NaOH was added dialkyl sulfate (0.08 mol) with magnetic stirring. The precipitate was filtered (Table I).

With Alkyl Halides (3-6, 24, and 26-29). To compound 1, 23, or 25 (0.07 mol) dissolved in DMF (50 mL) containing anhydrous K₂CO₃ (0.67 g, 0.07 mol) was added alkyl iodide (0.14 mol). The suspension was heated under reflux for 5 h or magnetically stirred for 20 h at room temperature. DMF was evaporated at reduced pressure, and the residue, after trituration with dilute HCl, was extracted with CHCl₃. The organic layer, dried on Na₂SO₄, was concentrated under vacuum. The gummy residue, after treatment with diethyl ether, was collected by filtration (Table I). In order to obtain 7-9 from 1 (0.07 mol), the suitable alkyl chloride (0.14 mol) in the presence of NaI (0.1 g, 0.66 mmol) was used as the alkylating agent.

The mixture of 26 and 28 underwent preparative TLC on silica gel (eluent CHCl₃/CH₃CN, 10:1). The first band consisted of pure 28; the second band yielded 26. Under the same conditions, 29 (the first band) was separated from 27 (the second band).

Ethyl 3-(4,7-Dihydro-7-oxo-2-phenylpyrazolo[1,5-*a*]pyrimidin-4-yl)propenoate (10). To 1 (1 g, 0.0047 mol) was added ethyl propenoate (10 mL). The solution was heated under reflux for 5 h. After the solution cooled, the resulting precipitate was collected by filtration (Table I).

3,6-Dibromo-4-ethyl-4,7-dihydro-2-phenylpyrazolo[1,5-*a*]pyrimidin-7-one (19) and 3-Bromo-4-ethyl-4,7-dihydro-2-phenylpyrazolo[1,5-*a*]pyrimidin-7-one (20). Method A. To 3 (2.39 g, 0.01 mol) suspended in CCl₄ (50 mL) were added *N*-bromosuccinimide (1.958 g, 0.011 mol) and benzoyl peroxide (0.1 g, 4 mmol). The mixture was heated under reflux for 4 h. The solvent was evaporated at reduced pressure, and the residue, containing both 19 and 20, was washed with water before filtration.

Method B. To 3 (1.19 g, 0.005 mol) suspended in CCl₄ (25 mL) was added Br₂ (0.86 g, 0.0054 mol) drop by drop at room temperature. A yellow precipitate formed. After filtration, the solid was dissolved in water and treated with a saturated solution of Na₂SO₃. Upon dilution, a white precipitate containing both 19 and 20 formed.

The above mixtures underwent preparative TLC on silica gel (eluent CHCl₃/CH₃CN 10:1). The first band consisted of 19; the second band yielded 20 (Table I).

4,7-Dihydro-2-phenyl-3-thiocyanatopyrazolo[1,5-*a*]pyrimidin-7-one (21). To 3 (0.59 g, 0.025 mol), dissolved in acetic acid (30 mL), was added Cu(SCN)₂ (1.79 g, 0.01 mol), which was prepared according to K. Fujiki.⁵ The suspension was stirred at 40-50 °C for 4 h. The filtered solution was diluted with water until a white precipitate formed (Table I).

Bis(4-Ethyl-4,7-dihydro-7-oxo-2-phenylpyrazolo[1,5-*a*]pyrimidin-3-yl) Disulfide (22). A solution of 21 (1.47 g, 0.05 mol) in 4% KOH (12.5 mL) and CH₃OH (30 mL) was magnetically stirred until a yellow precipitate formed, which was collected by filtration (Table I).

4,7-Dihydro-3-nitroso-2-phenylpyrazolo[1,5-*a*]pyrimidin-7-one (23). To 1 (10 g, 0.05 mol) dissolved in the least amount of warm acetic acid/HCl (20:1) was added an excess of solid NaNO₂. The deep-green precipitate, after filtration, was thoroughly washed with water (Table I).

Carrageenin-Induced Edema of the Rat Paw. Antiinflammatory activity was examined by the method of Winter et al.⁷ A group of five female rats weighing 120-150 g were dosed orally

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Table V. Toxicological Properties and Safety (TI) of Some 2-Phenylpyrazolo[1,5-a]pyrimidine Compounds

compd	ulcerogenic act.			acute toxicity				TI ^d					
	dose, mg/kg, po	UI ^a	UD ₅₀ ^{b,c} mg/kg	dose, mg/kg, ip	died 72nd h	%	LD ₅₀ ^b mg/kg						
indomethacin	5	1.4 ± 0.31	12.1 (4.8-30.3)	8	1/7	14.2	19.9 (10.3-38.5)	10.9					
	30	2.36 ± 0.24		12	2/7	28.5							
	50	3.3 ± 1.04		15	3/7	42.8							
phenylbutazone	50	1.35 ± 0.27	72.4 (46-116)	75	7/7	100.0	238.2 (210-305.8)	18.2					
	100	2.55 ± 0.13		170	0/7	0.0							
	200	3.20 ± 0.13		225	2/7	28.5							
				300	4/7	57.1							
2	150	0.5 ± 0.12		350	7/7	100.0	126.6 (116-138.4)	5.13					
				100	0/7	0.0							
				115	1/7	14.2							
				120	3/8	37.5							
				130	4/7	57.1							
				150	6/7	85.7							
				200	0/7	0.0							
3	150	0.15 ± 0.04		250	1/7	14.3	270.6 (244-307.1)	37.1					
				260	2/7	28.5							
				270	3/6	50.0							
				280	5/7	71.4							
				contr + stress	0.68 ± 0.07								

^a UI = ulcer index.¹⁰ ^b 95% confidence limits in parentheses. ^c UD₅₀ = median ulcerogenic dose. ^d TI = therapeutic index (LD₅₀/ED₅₀ carr).

with a suspension of the test compound 1 h before injection of 0.05 mL of a suspension of carrageenin in 0.9% NaCl solution into the right and left hind paws. Controls had suspension vehicle. Three, four, five, and six hours later, paw volumes were measured by plethysmography, and results were expressed as the percent of reduction of edema in comparison with the controls.

Analgesic Activity. Analgesic activity was evaluated by the acetic acid induced writhing method.⁸ Ten male mice weighing 18-22 g were used in each group. The test compound was dosed orally in 0.25 mL of Carbowax (1%) suspension 1.5 h before intraperitoneal injection of acetic acid (0.75%). The number of writhes in the following 15 min was recorded. Results are expressed as percent reduction of writhes attributable to drug treatment in comparison with the controls (vehicle alone).

Adjuvant Arthritis Assay.⁹ Five male rats weighing 100 g were used in each group. On day 1, 0.1 mL of a suspension of Freund's complete adjuvant DIFCO was injected into the left hind paw of each rat. The rats were then kept in cages, two to three rats per cage, for 20 days. All animals that developed arthritis were used in this study. At 20 days, the foot volumes were measured, and the compound was administered by gavage between days 20 and 23. The decrease or increase in the paw volume of the groups treated with the compounds under examination on the 23rd day was evaluated with reference to the value of the percent increase in a group of animals treated with the adjuvant alone and a group of animals who received no treatment at all.

Acute Ulcerogenicity. Male rats weighing 180-200 g were used in this study and starved for 24 h. Water was given ad libitum. Before the experiments, the animals were orally dosed with test compound suspended in 1% Carbowax solution. Restrain stress was induced by wrapping the animals individually in a plaster bandage and placing them in a warm (25 °C) room for the duration of the experiment (2 h). At the conclusion of the experiment, the rats were killed, and their stomachs were excised and opened along the greater curvature. The number and severity of the lesions were assessed on an arbitrary scale of 0 to 4 according to the literature.¹⁰

Acute Toxicity. Acute toxicity was expressed as an LD₅₀ value calculated by the method of Litchfield and Wilcoxon.¹¹ It was determined after an intraperitoneal injection of the test compound in mice (Table V).

Acknowledgment. Mass spectral analyses were carried out at the "Centro di Spettrometria di Massa" della Facoltà di Medicina, Università di Firenze.

Registry No. 1, 77493-73-3; 2, 77494-10-1; 3, 86969-15-5; 4, 77494-11-2; 5, 86969-16-6; 6, 86969-17-7; 7, 86969-18-8; 8, 86969-19-9; 9, 86969-20-2; 10, 86969-21-3; 11, 65774-88-1; 12, 27232-23-1; 13, 86969-22-4; 14, 86969-23-5; 15, 86969-24-6; 16, 86969-25-7; 17, 29274-23-5; 18, 77494-09-8; 19, 86993-45-5; 20, 86969-26-8; 21, 86969-27-9; 22, 86969-28-0; 23, 86969-29-1; 24, 86969-30-4; 25, 79039-17-1; 26, 86969-31-5; 27, 86969-32-6; 28, 86969-33-7; 29, 86969-34-8; ethyl propynoate, 623-47-2; *N*-bromosuccinimide, 128-08-5; Cu(SCN)₂, 15192-76-4.

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