Cycloaddition of Acetylenes to 7-Acylamino-3-azidomethyl-3-cephem-4-carboxylic Acids

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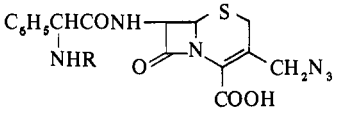
A series of 7-acylamino-3-(1,2,3-triazol-1-ylmethyl)-3-cephem-4-carboxylic acids was prepared by the cycloaddition of acetylenes to 7-acylamino-3-azidomethyl-3-cephem-4-carboxylic acids or esters. Although such a dipolar reaction can yield two positional isomers when a monosubstituted acetylene is used, only one isomer was detected except in the case of ethoxyacetylene. The 7-acylamino moieties included D-phenylglycyl which can affect favorably the antimicrobial spectrum and oral absorption of a β-lactam compound; however, none of the compounds was orally effective in the mouse. Representative *in vitro* antibacterial data are given.

A recent report[1] from these laboratories has described the synthesis of 7-(D-α-aminophenylacetamido)-3-azidomethyl-3-cephem-4-carboxylic acid (I), a semisynthetic cephalosporin which possessed broad-spectrum antibacterial activity and was effectively absorbed orally in the mouse. Thus, compound I provided another striking example of the ability of the 7-D-phenylglycyl moiety to confer the desirable properties of combined Gram-negative activity and oral absorbability on a 3-cephem nucleus bearing an appropriate substituent in the 3 position.[2]



I, R = H
II, R = $COOC(CH_3)_3$ (BOC)

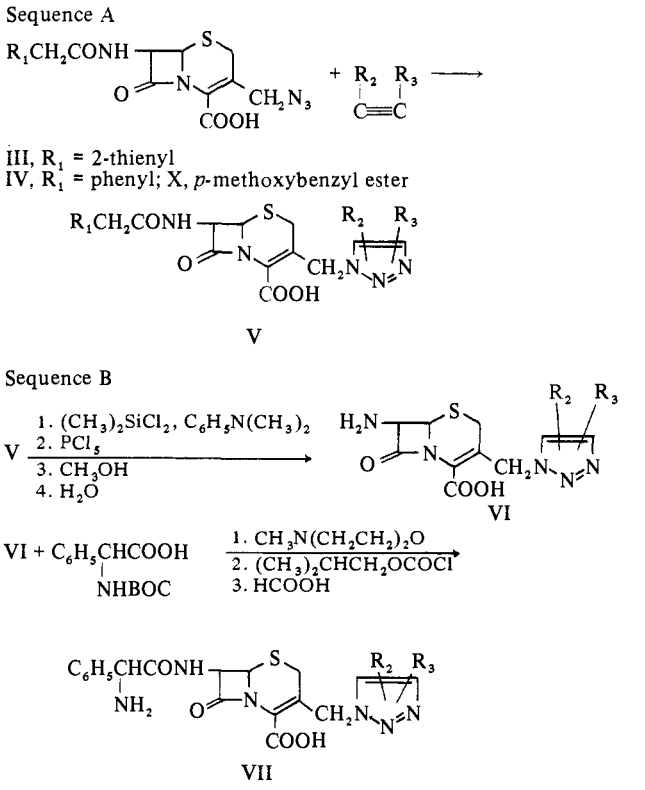
Because alkyl azides are remarkably reactive toward various reagents,[3-5] we have explored the feasibility of transforming the azido group of I into novel 3-substituted cephalosporin derivatives relatively inaccessible by direct displacement of the acetoxy group. We now report the synthesis and antibacterial activity of 20 7-acylamino-3-(1,2,3-triazol-1-ylmethyl)-3-cephem-4-carboxylic acids (Table I) obtained *via* the cycloaddition of substituted acetylenes to 3-azidomethyl-7-(2-thienylacetamido)-3-cephem-4-carboxylic acid (III)[6] (Scheme I) or 3-azidomethyl-7-phenylacetamido-3-cephem-4-carboxylic acid (IV)[7] *p*-methoxybenzyl ester (X).

After the completion of this series, a patent[8] appeared that disclosed similar syntheses; however, all of the compounds described with one exception (**1**, Table I) are different from ours, and none contains the D-phenylglycyl moiety.

Chemistry. In early experiments the direct reaction of monosubstituted acetylenes with I or II as the free acids was unsatisfactory; likewise unfavorable results were obtained with 7-amino-3-azidomethyl-3-cephem-4-carboxylic acid.[1,9] We used, therefore, the synthetic route shown in Scheme I. Sequence A was used to prepare compounds **1**–**7** (Table I). Except for the preparation of **2**, all syntheses were carried out without solvents, usually at room temperature.

The triazoles in **3**–**7** were derived from monosubstituted acetylenes *via* a cycloaddition which could form one isomer or a mixture of two positional isomers. It is known[4,10] that the direction of these dipolar additions is determined by both electronic and steric factors. In this case, examination of the crude reaction mixtures of **3**–**7** by tlc and nmr indicated the presence of only one component, and only one isomer was isolated in crystalline form. We have not made definite isomeric assignments (see Scheme I and Table I); however, by analogy with other cases[4,10] and using **3** as an example, the structure of the triazole should be as shown in VIII. Likewise, **8**, which was prepared from ethoxyacetylene, should be represented by IX; in this case, however, tlc and nmr showed the presence of *ca.* a 1:1 mixture of isomers. Only one of these, with an as yet unknown substitution pattern, was isolated. It should be noted, however, that the reaction conditions were atypical (see Experimental Section).

Scheme I



To obtain **8**, **9**, **10**, and **11**, the *p*-methoxybenzyl ester (X) was advantageously used in place of the less soluble IV to effect the cycloaddition, followed by cleavage of the ester group with trifluoroacetic acid to obtain the product (V).

As a safety precaution, we avoided the direct reaction of acetylene with IV. Instead, **9** was prepared by decarbonylation[11] of the adduct obtained from X and propiolaldehyde.[12]

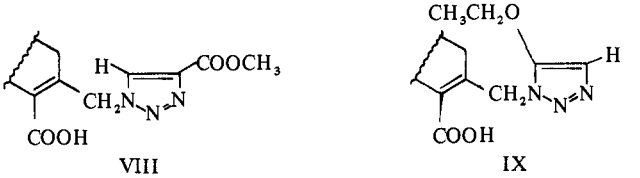
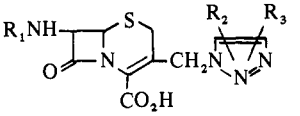
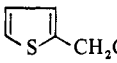


Table I



R_1	Compd	R_2	R_3	Sequence	Mp, °C	Formula	Analyses
	1	CO_2CH_3	CO_2CH_3	A	80–84	$C_{20}H_{19}N_5O_8S_2$	C, H, N
	2	CO_2H	CO_2H	A[a]	72–78	$C_{18}H_{15}N_5O_8S_2$	C, H, N
	3	CO_2CH_3	H	A	164[f]	$C_{18}H_{17}N_5O_6S_2$	C, H, N
	4	CO_2H	H	A	193–195[f]	$C_{17}H_{15}N_5O_6S_2$	C, H, N
	5	CH_2OH	H	A	154[f]	$C_{17}H_{17}N_5O_5S_2$	C, H, N
	6	CHO	H	A	143	$C_{17}H_{14}N_5O_5S_2K$	C, H, N
	7	$COCH_3$	H	A	162	$C_{18}H_{16}N_5O_6S_2K$	C, H, N
$C_6H_5CH_2CO$	8	OCH_2CH_3[b]	H	A[c]	194	$C_{20}H_{21}N_5O_5S$	C, H, N
	9	H	H	A[c,d]	115–119	$C_{18}H_{17}N_5O_4S$	C, H, N
	10	CF_3	CF_3	A[c,e]	164	$C_{20}H_{15}F_6N_5O_4S$	C, H, N
	11	CF_3	CF_3	A[c]	112	$C_{20}H_{15}F_6N_5O_4S$	C, H, N
$C_6H_5CH(NH_2)CO$	12	CO_2CH_3	CO_2CH_3	A–B	210	$C_{22}H_{22}N_6O_8S$	C, H, N
	13	CO_2H	CO_2H	A–B	189–201	$C_{20}H_{18}N_6O_8S$	C, H, N
	14	CO_2CH_3	H	A–B	181–183	$C_{20}H_{20}N_6O_6S$	H, N, C[g]
	15	CO_2H	H	A–B	189	$C_{19}H_{18}N_6O_6S$	C, H, N
	16	$COCH_3$	H	A–B	216	$C_{20}H_{20}N_6O_5S$	H, N, C[h]
	17	CH_2OH	H	A–B	168	$C_{19}H_{20}N_6O_5S$	C, H, N
	18	OCH_2CH_3	H	A–B	154–159	$C_{20}H_{22}N_6O_5S$	C, H, N
	19	H	H	A–B[d]	187	$C_{18}H_{18}N_6O_4S$	H, N, C[i]
	20	CF_3	CF_3	*d*	158–161	$C_{20}H_{16}F_6N_6O_4S$	C, H, N

[a]The reaction was carried out in DMF solution. [b]A mixture of positional isomers, one of which was isolated. [c]The *p*-methoxybenzyl ester of IV was used for the cycloaddition with the acetylene. [d]See full text and Experimental Section. [e]This is the Δ^2 compound. [f]The mp is that of the potassium salt. [g]C: calcd, 50.84; found, 50.17. [h]C: calcd, 52.63; found, 51.89. [i]C: calcd, 52.17; found, 49.10.

Table II. Antimicrobial Activity[a]

Compd	*Diplococcus pneumoniae* (A9585)	*Streptococcus pyogenes* (A9604)	*Staphylococcus aureus* Smith (A9537)	*Salmonella enteritidis* (A9531)	*Escherichia coli* Juhl (A15119)	*Klebsiella pneumoniae* (A9977)	*Proteus mirabilis* (A9900)
1	0.02	0.16	0.16	0.6	32	8	4
2	0.25	0.5	1.3	1.3	32	32	8
3	0.005	0.005	0.08	0.5	16	4	4
4	0.6	0.6	0.3	2	125	4	1
5	0.08	0.08	0.16	2	32	4	2
6			0.16	1	63	8	4
7			0.04	0.25	16	4	4
8	0.08	0.08	0.08	2.5	125	32	16
9	0.04	0.04	0.04	1.3	125	16	4
10	2.5	2.5	2.5	125	125	125	125
11	0.04	0.04	0.16	4	125	32	63
12	10	10	10	32	125	125	125
13	2.5	2.5	2.5	4	16	16	4
14	0.08	0.08	0.6	1	4	2	2
15	0.6	0.6	2.5	4	4	4	4
16		0.3	2.5	8	16	8	8
17	1.3	0.3	2.5	8	16	8	8
18	0.6	0.6	1.3	1.3	16	4	4
19	0.16	0.16	0.16	4	8	4	4
20	0.6	0.6	2.5	8	125	16	125
Cephalothin	0.08	0.08	0.16	0.3	16	1	1

[a]The antimicrobial activity is given as the minimum inhibitory concentration (MIC) in μg/ml. The MIC's were determined by the twofold tube dilution method in nutrient broth (Difco) except for *D. pneumoniae* and *Strep. pyogenes* which were determined in a 1:1 mixture of nutrient broth and antibiotic assay broth (BBL) supplemented with 5% human serum (see ref 1).

The cycloaddition of X with hexafluorobutyne-2 yielded a mixture of the Δ^2- and Δ^3-cephem compounds. These, after separation, were converted to **10** and **11**.

Compounds **1–9** served as intermediates for the preparation of **12–19** *via* sequence B. Cleavage of the acyl groups from III and IV was accomplished *via* silyl esters of the starting acids.[13,14] Condensation of VI with D-BOC-phenylglycine *via* a mixed anhydride was carried out with minimal or no racemization[1] at the α-amino carbon. Compound **20**, on the other hand, was prepared by the direct cycloaddition of hexafluorobutyne-2 to the *p*-methoxybenzyl ester (XI) of II with subsequent removal of the protective groups.

The ir and nmr data of all compounds were consistent with structure. It was interesting to note that the exocyclic-methylene hydrogens undergo a downfield shift in their nmr absorption after the formation of the triazole. In the starting materials, they absorbed at 3.7–4.2 ppm. The variations depended on several factors such as on the nature of the 7-*N*-acyl moiety, on whether the spectra were determined on the free acid, salt, or ester, and on the nature of

the solvent. After the cycloaddition to acetylenes the exocyclic hydrogen atoms absorbed at 5.3–5.5 ppm. This shift might be attributed to the presence of the new adjacent aromatic system.

Antimicrobial Activity. The antimicrobial activity of compounds **1–20** against several microorganisms is given in Table II. One notices the relatively high antibiotic activity of compound **10**, a Δ^2-cephalosporin. While the possibility that the sample is contaminated with the Δ^3 isomer cannot be absolutely ruled out (see Experimental Section), our analytical data (ir, nmr, tlc) militate against this possibility.

Those compounds which possess a phenylglycyl moiety were examined for oral activity in the mouse. The oral blood levels obtained with these compounds were only 0.8–16.6% those of cephalexin when given at 100 mg/kg. Compounds **14**, **16**, and **17** were also examined for their oral CD_{50} values against *Streptococcus pyogenes* (A9604). These were 2, 15, and 11 times, respectively, higher than those of cephalexin.

Experimental Section

Mps were detd in capillaries on a Mel-Temp apparatus and are uncorrected. Ir spectra were obtained on a Perkin-Elmer 257 spectrometer in KBr pellets. Nmr spectra were obtained on a Varian A-60 spectrometer. Spectra of 1–11 were detd in CD_3COCD_3, those of **12–20** in CD_3COCD_3–DCl. Solvents were evapd under reduced pressure in a rotary evaporator. Tlc spots were detected by uv. All acetylenes were commercially available, except for propiolaldehyde which was prepd according to the literature.[12] Where analyses are indicated by symbols of elements only, analytical results obtained for those elements were within ±0.4% of the theoretical values.

3-(4,5-Dimethoxycarbonyl-1,2,3-triazol-1-ylmethyl)-7-(2-thienylacetamido)-3-cephem-4-carboxylic Acid (1). Sequence A. A mixt consisting of 3.79 g (0.01 mole) of III[6] and 25 ml of dimethyl acetylenedicarboxylate was stirred at room temp under anhyd conditions for 21 hr. The mixt was poured into 300 ml of anhyd Et_2O. The ppt was collected by filtration and washed well several times with 50-ml portions of anhyd Et_2O. It melted at 80–84°. Ir and nmr were consistent with structure; 1.69 g (32.1%).

For the prepn of the potassium salts, 0.004 mole of the crude free acid was dissolved in 10 ml of *n*-BuOH and 1 ml of Me_2CO. To the cooled soln was added 4 ml of a 1 *N* soln of potassium 2-ethylhexanoate in *n*-BuOH (KEH). Crystn was induced by cooling and scratching, and the crystals were collected by filtration and washed well with cold Me_2CO.

7-(D-α-Aminophenylacetamido)-3-(4,5-dimethoxycarbonyl-1,2,3-triazol-1-ylmethyl)-3-cephem-4-carboxylic Acid (12). Sequence B.

(a) Cleavage of the 2-Thienylacetyl Moiety; Prepn of VI. A mixt of 3.38 g (0.0065 mole) of 1 and 26 ml of dry CH_2Cl_2 was stirred and to this was added in succession 0.9 ml (0.0067 mole) of Et_3N, 1.6 ml (0.0127 mole) of $C_6H_5NMe_2$, and 0.68 ml (0.0054 mole) of Me_2SiCl_2. After stirring for 30 min, the soln was cooled to −50°, and 1.47 g (0.0070 mole) of PCl_5 was added. The soln was stirred for 2.5 hr at −40°. Then, at −60°, 0.4 ml of $C_6H_5NMe_2$ was added, followed by 10 ml of cold MeOH. The mixt was stirred for 3 hr at −50° and poured into 16 ml of H_2O, and the mixt was brought to pH 4 with 6 *N* NH_4OH. The mixt was kept cold for 1 hr. The ppt was collected by filtration, washed with two 20-ml portions of CH_2Cl_2, and dried; 1.61 g (62.8%).

(b) Coupling of VI with D-BOC-phenylglycine. Under anhyd conditions a soln of 0.91 g (0.0036 mole) of D-BOC-phenylglycine[15] in 25 ml of dry THF was stirred and cooled to −15°. *N*-Methylmorpholine (0.31 g, 0.0031 mole) and then 0.56 g (0.004 mole) of $(CH_3)_2CHCH_2OCOCl$ were added. After 4 min, an ice-cold soln of 1.2 g (0.003 mole) of VI and 0.31 g (0.003 mole) of *N*-methylmorpholine in 30 ml of H_2O was added all at once to the mixed anhydride. The reaction mixt was allowed to warm to room temp while being stirred. The THF was evapd, the aqueous soln was layered with 20 ml of EtOAc and acidified to pH 2 with 42% H_3PO_4. The extn was repeated, and the combined exts were washed (H_2O), dried ($MgSO_4$), and evapd. The foam was dissolved in a small vol of EtOAc and added to 500 ml of cyclohexane. The solid was collected by filtration and air-dried. It was dissolved in 25 ml of 97% HCOOH and stirred for 2 hr at room temp under anhyd conditions. The soln was poured into 300 ml of anhyd Et_2O. The Et_2O was decanted, and the ppt treated several times in the same manner with Et_2O. The product **12** was finally collected by filtration and dried at high vac, 0.45 g (25%). Ir and nmr were consistent with structure.

***p*-Methoxybenzyl 3-Azidomethyl-7-phenylacetamido-3-cephem-4-carboxylate (X).** A soln of 38.3 g (0.1 mole) of the Na salt of 3-azidomethyl-7-phenylacetamido-3-cephem-4-carboxylic acid[7] (IV) in 230 ml of $CH_3CON(CH_3)_2$ (DMAC) was stirred vigorously, and 26.1 g (0.13 mole) of *p*-methoxybenzyl bromide[16] was added to it. The mixt was stirred overnight at room temp under anhyd conditions. The mixt was poured into a soln of 1500 ml of Skellysolve B and 250 ml of Et_2O. The mixt was stirred for 1 hr, and the solvent decanted. The residue was mixed with EtOAc and a 10% $NaHCO_3$ soln. The organic layer was sepd, washed (H_2O), and dried ($MgSO_4$), and the solvent evapd. The residue was triturated with anhyd Et_2O to yield a white cryst mass, which was collected by filtration and air-dried, mp 118°, 34.1 g (71%). Ir and nmr were consistent. *Anal.* ($C_{24}H_{23}N_5O_5S$) C, H, N.

Cycloaddition of X with Ethoxyacetylene; Preparation of 8. A mixt of 4.98 g (0.012 mole) of X, 1.96 g of ethoxyacetylene, and 8 ml of C_6H_6 was heated under reflux at 110° for 18 hr. The excess of the acetylene and C_6H_6 was evapd, and the residue crystd from C_6H_6. Nmr and tlc indicated the presence of 2 isomers in approx equal amts. The material was then fractionally recrystd from Me_2CO to yield one pure isomer, mp 179–182° dec. This isomer, 1.12 g (0.002 mole), was treated with a cold mixt of 4 ml of anisole and 20 ml of CF_3COOH. The soln was stirred for 1 hr under anhyd conditions and poured into a mixt of 100 ml of Skellysolve B and 1 ml of Et_2O. The solid, collected by filtration, was dissolved in 50 ml of 5% $NaHCO_3$. The soln was filtered and acidified with 42% H_3PO_4. The solid was collected and air-dried to yield 140 mg of **8**. The other isomer could not be isolated pure.

7-Phenylacetamido-3-(1,2,3-triazol-1-ylmethyl)-3-cephem-4-carboxylic Acid (9). A mixt of 1.47 g (0.0035 mole) of X, 0.59 g (0.011 mole) of propiolaldehyde, and 2.4 ml of C_6H_6 was heated under reflux for 55 min. The mixt was evapd, dissolved in Me_2CO, and evapd again. The residue was dissolved in hot *i*-PrOH. Upon cooling an amorphous ppt was formed which was collected by filtration.

For the decarbonylation reaction,[11] a soln of 4.0 g (0.008 mole) of the amorphous ppt and 7.59 g (0.0082 mole) of $RhCl[P(C_6H_5)_3]_3$ in 30 ml of dry C_6H_6 was refluxed for 2 hr. The ppt that formed upon cooling was collected by filtration and redissolved in 50 ml of Me_2CO, and the soln filtered. The solvent was evapd, and the residue extd with hot *i*-PrOH. The soln was filtered and cooled. A fine cryst ppt was formed, and it was collected by filtration. For further purification, the solid was triturated with methyl isobutyl ketone (MIBK) to yield 2.73 g (71%), mp 115–119°. Ir and nmr were consistent. The protective ester was removed with anisole and CF_3COOH as described in the previous expt to yield **9**.

Condensation of X with Hexafluorobutyne-2; Preparation of 10, 11. Into a round-bottom flask equipped with a stirrer and a Dry Ice–acetone condenser was placed a soln of 9.6 g (0.02 mole) of X in 125 ml of dry toluene. The soln was cooled to −50°, and 23.0 g (0.142 mole) of $CF_3C{\equiv}CCF_3$ was dissolved in it. The mixt was stirred and heated at 85° (oil bath) for 19 hr. The soln was cooled to 10°, and the solid collected. It was crystd from C_6H_6 to yield 5.3 g, mp 169°. *Anal.* ($C_{28}H_{23}F_6O_5N_5S$) C, H, N. The nmr indicated that this was a pure sample of the Δ^2 isomer of the *p*-methoxybenzyl ester (XII) of **10**. Hydrolysis with CF_3COOH gave **10**.

The mother liquor was evapd, and the residue extd with 100 ml of C_6H_6. The solvent was evapd. Part of the solid, 2 g, was chromatographed over a 5 × 25 cm column of silica gel (SilicAR, CC-7 100–200 mesh) using C_6H_6–Me_2CO (91:9) as solvent. The fractions, 10–15 ml each, were monitored by tlc. In this manner, 0.98 g of pure Δ^3-ester was obtained which was hydrolyzed to yield **11**.

***N,N*-Dibenzylethylenediammonium 3-Azidomethyl-7-(D-α-*tert*-butoxycarboxamidophenylacetamido)-3-cephem-4-carboxylate.** A soln of 33.8 g (0.0694 mole) of II in 270 ml of Me_2CO was refluxed gently, and a soln of 8.4 g (0.035 mole) of *N,N*-dibenzylethylenediammonium diacetate in 150 ml of H_2O was added. The hot soln was filtered, and the filtrate cooled in an ice bath. The solid was collected by filtration, yield 17.8 g, mp 170–178°. An addnl crop of 3.6 g could be obtained by concg the soln (25.2%).

***p*-Methoxybenzyl 3-Azidomethyl-7-(D-α-*tert*-butoxycarboxamidophenylacetamido)-3-cephem-4-carboxylate (XI).** This was prepared essentially as described for X from 5.94 g (0.005 mole) of the above described salt and 2.211 g (0.011 mole) of *p*-methoxybenzyl bromide[16] in 25 ml of DMAC. The cryst ester weighed 1.4 g (23.3%), mp 74–78°; ir and nmr were consistent. *Anal.* ($C_{29}H_{32}N_6O_7S$) C, H, N.

7-(D-α-Aminophenylacetamido)-3-(4,5-bis(trifluoromethyl)-1,2,3-triazol-1-ylmethyl)-3-cephem-4-carboxylic Acid (20). The condensa-

tion was carried out as described for compd 10 from 1.80 g (0.003 mole) of XI and 1.62 g (0.010 mole) of $CF_3C{\equiv}CCF_3$. After heating at 80° for 5 hr, the reaction was complete (tlc). The reaction mixt was cooled, and the cryst ppt was collected by filtration. There was obtained 1.82 g (79%) of the triazole ester (XIII), mp 167–168°; ir and nmr were consistent. *Anal.* ($C_{33}H_{32}F_6N_6O_7S$) C, H, N.

The ester, 0.5 g, was dissolved in 20 ml of CF_3COOH contg 1 drop of anisole. The soln was stirred at 0–10° for 1 hr and then poured into a mixt of 20:70 Et_2O–Skellysolve B. The ppt was collected by filtration to yield 0.332 g of crude **20**. This was purified in the following manner. The material was suspended in 20 ml of H_2O and heated to 60°. Then 0.19 g of $TsOH \cdot H_2O$ was added, and the clear soln was filtered and cooled. The cryst ppt was collected by filtration. This solid was dissolved in a small vol of H_2O at 70° and filtered, and the pH adjusted to 4.1 with Et_3N. On cooling, a cryst ppt of **20** was formed which was collected and dried, 0.170 g (44.3%), mp 158–161°; ir and nmr were consistent.

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Schistosomicidal 5-Nitro-4-thiazolines

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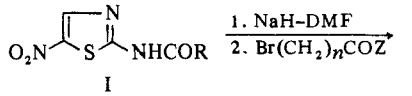
Various 2-(acyl- and alkoxycarbonylimino)-5-nitro-4-thiazoline-3-acetamides (III, Z = NR_1R_2; n = 1) and the corresponding 4-thiazoline-3-acetic acid esters (III, Z = alkoxy; n = 1) were prepared by alkylation of the sodium salt of the appropriate 2-acylamido-5-nitrothiazole or 5-nitro-2-thiazolecarbamic acid ester with a 2-bromoacetamide or bromoacetate in *N,N*-dimethylformamide. Many of these 5-nitro-4-thiazolines showed potent schistosomicidal activity, effecting a 50–100% reduction of adult *Schistosoma mansoni* in mice at daily doses of less than 400 mg/kg for 14 days.

Continuing our investigations on derivatives of 2-amino-5-nitrothiazole as potential schistosomicides[1] the alkylation of 2-acetamido-5-nitrothiazole with substituted bromoacetamides was examined. In contrast with previous work with 2-formamido-5-nitrothiazole wherein alkylation took place almost exclusively on the amide nitrogen to give derivatives of type II, similar treatment of 2-acetamido-5-nitrothiazole provided iminothiazolines (III) as a result of alkylation on the thiazole ring nitrogen. Surprisingly, it was found that, in contrast to the minimal activity of II, the iminothiazolines III were extremely potent against *Schistosoma mansoni* infections in experimental animals.

The present communication presents the results of the investigation of this novel lead and describes the preparation of various 2-(acyl- and alkoxycarbonylimino)-5-nitro-4-thiazoline-3-acetamides (III, Z = NR_1R_2; n = 1) and the corresponding 4-thiazoline-3-acetic acid esters (III, Z = alkoxy; n = 1), together with several of the analogs (III, n = 2 and 3). Extension of this series to the related system IV is described in the subsequent paper.[2]



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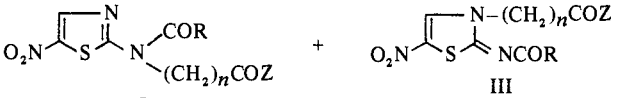
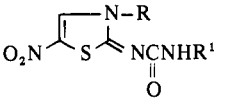


II III

Chemistry. Thiazolines (III, n = 1) (**1–10**, **13–21**, **23–38**, **46–51**, **53–58**, and **60**, Table I) and the α-methyl analog **11** were obtained in 2–73% yield by alkylation of a DMF solution of the sodium salt of the appropriate amide or carbamic acid ester I with a bromoacetamide or bromoacetate. The alkylation process gave varying amounts of thiazoline III together with the thiazole isomer II; however, the required thiazolines were obtained in a pure state relatively easily in most cases by fractional crystallization (accompanying thiazoles II were not purified in most cases).



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