# Chemistry of Cephalosporin Antibiotics. 28. Preparation and Biological Activity of 3-(Substituted)vinyl Cephalosporins<sup>1</sup>

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3-(Substituted)vinylcephem nuclei have been prepared by the reaction of 3-formylcephem derivatives with stabilized phosphoranes. Appropriate synthetic steps allowed preparation of a series of 3-ethoxycarbonylvinyl- and 3-carboxy-vinylcephem derivatives bearing a variety of 7-acylamino functions. The phenoxyacetyl and thiopheneacetyl derivatives of the 3-cyanovinylcephem nucleus were also prepared. Although general gram-positive activity was comparable to cephalothin in many cases, against penicillin G resistant *Staphylococcus aureus*, the new cephalosporins were of low effectiveness. The 3-(substituted)vinyl cephalosporins had good activity against a number of gram-negative organisms. In some cases, this activity was excellent. The N-acetyl analogs had surprisingly good activity relative to N-acetyl-7-ACA. The phenylmalonoyl side-chain derivatives were shown to have an unusual antibacterial spectrum expansion (relative to previously known cephalosporins) to include activity against *Serratia marcescens* and *Pseudomonas aeruginosa*.

In a search for unique and desirable cephalosporin antibiotics, we have prepared a series of 3-(substituted)vinylcephem derivatives. Previously synthesized cephalosporins have usually had a saturated carbon<sup>2</sup> (C-3') attached to position 3 of the cephem nucleus. We thought that converting this C-3' to an sp<sup>2</sup> center might bring about interesting biological activity<sup>3</sup> changes.

The 3-(substituted)vinyl moiety was generated by reaction of 3-formylcephem derivatives<sup>2a,4</sup> with stabilized phosphoranes.<sup>5</sup> Our initial lead, 3-ethoxycarbonylvinyl-7-phenoxyacetamido-3-cephem-4-carboxylic acid (5a), was prepared as outlined in Scheme I. The in vitro antibacterial activity, as determined in gradient plate assay,<sup>6</sup> for compound 5a is indicated in Table I, with comparison data for other phenoxyacetamidocephem acids. Structure-activity relationships of the cephalosporin antibiotics have indicated that derivatives bearing the phenoxyacetyl side chain retain significant activity against penicillin G resistant staphylococcus but have poor gram-negative activity. This is illustrated in Table I. The comparatively significant gram-negative activity of 5a was encouraging and suggested that a derivative with an appropriate 7-amino side chain might possess excellent gram-negative activity. The poor penicillin-resistant staphylococcus activity of 5a and related compounds will be discussed below.

Chemistry. Synthesis of additional 3-(substituted)vinylcephem nuclei was attempted by reacting the 3-formylcephem sulfoxide ester 2 with stabilized phosphoranes<sup>7</sup> other than the commercially available (ethoxycarbonylmethylene)triphenylphosphorane. Scheme I summarizes our successful attempts. The tert-butyl ester, which was utilized as a precursor to carboxyl, series **b**, derived from (tert-butoxycarbonylmethylene)triphenylphosphorane<sup>8</sup> gave results equally as good as the ethyl ester series  $\mathbf{a}$ . In both series exclusively trans configuration,  $J_{\text{vinyl H}} = 16$ Hz, was observed. The cyano series c, from (cyanomethylene)triphenylphosphorane,<sup>7a</sup> gave significantly lower yields and a cis-trans mixture<sup>9</sup> (ca. 3:2;  $J_{cis} = 12$  Hz,  $J_{trans}$ = 16 Hz). Experiments using (carbamylmethylene)triphenylphosphorane<sup>7b</sup> gave no isolable product upon reaction with aldehyde 2; (formylmethylene)triphenylphosphorane<sup>7c</sup> gave very low yields of two cephalosporin products, suggesting a cis-trans mixture, but no definitive characterization could be made, possibly because of lability of products; (methylcarbonylmethylene)triphenylphosphorane<sup>7d</sup> gave a low yield of material characterized by NMR as having vinyl protons (J = 16 Hz) and a methyl ( $\delta$  2.5) suggestive of an  $\alpha,\beta$ -unsaturated methyl ketone. Deesterification of this material gave an impure cephem acid with only very weak activity.

As indicated in Table IV and the Experimental Section,





Table I. Gradient Plate Activity of Selected Phenoxyacetamidocephems



				Gra	un-negative				
Z	Resistant S. aureus <sup>a, b</sup>	Shig.	E. coli	K. pn.	Ent. aerog.	Sal. heid.	S. marces.	P. aerug.	
CH <sub>2</sub> OAc	0.5	>50	>50	20.3	>50	>50	>50	>50	
CH	1.5	>50	>50	>50	>50	>50	>50	>50	
CH <sub>2</sub> OCH <sub>2</sub> <sup>d</sup>	0.2	>50	>50	>50	>50	>50	>50	>50	
CH,SCH,	0.2	>50	>50	>50	>50	>50	>50	>50	
CH <sub>2</sub> CN <sup>7</sup>	0.5	>50	>50	27.8	>50	>50	>50	>50	
CH <sub>2</sub> NO <sub>2</sub>	2.8	>50	>50	>50	>50	>50	>50	>50	
$CH = CHCO_2Et$ (5a)	4.8	16.4	17.9	7.6	16.3	20.3	>50	>50	

<sup>a</sup>MIC in  $\mu$ g/ml. <sup>b</sup>Average value using three penicillin G resistant, coagulase-positive, Staphylococcus aureus strains. <sup>c</sup>Shig. = Shigella species, E. coli = Escherichia coli, K. pn. = Klebsiella pneumoniae, Ent. aerog. = Enterobacter aerogenes, Sal. heid. = Salmonella heidelberg, S. marces. = Serratia marcescens, P. aerug. = Pseudomonas aeruginosa. <sup>a</sup>J. A. Webber et al., J. Med. Chem., 14, 113 (1971). <sup>e</sup>C. F. Murphy and R. E. Koehler, unpublished results. <sup>f</sup>J. A. Webber and R. T. Vasileff, J. Med. Chem., 14, 1136 (1971). <sup>e</sup>J. A. Webber and R. T. Vasileff, unpublished results.

these 3-(substituted)vinylcephem compounds have uv spectra, ca.  $\lambda_{max}$  320 nm with  $\epsilon$  in the range 15,000–25,000, significantly different than those observed<sup>9</sup> in older cephem derivatives. In the majority of cases, we did not observe a shoulder in the usual cephem uv absorption range of  $\lambda_{max}$  265–275 nm.

The cephem nuclei 6 were acylated and then deesterified to give a series of 7-acylamino-3-(substituted)vinylcephem acids. Some derivatives were prepared by analogy to the method of Scheme II, exemplified for the N-tert-butyloxy-

Scheme II



carbonylphenylglycyl side chain. Antibacterial activity of the new compounds prepared is presented in Tables II and III.

**Biological Results and Discussion.** Table II summarizes the gram-positive activity for selected 3-(substituted)vinylcephem acids. The trend toward weaker penicillinresistant staphylococcus activity than usually observed in cephalosporins (e.g., cephalothin) held throughout the series of new derivatives. However, as indicated by the diskplate<sup>10</sup> zone sizes, many of the new compounds had activity against penicillin-sensitive staphylococcus, *Bacillus subti*-

 Table II. Gram-Positive Activity of Selected

 3-(Substituted)vinylcephems

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	Resistant	Disk zone size, mm <sup>c</sup>					
Compound <sup>a</sup>	MIC, μg/ml	Sensitive S. aureus	B. subtilis	S. Iulea			
Cephalothin	0.4	28	44	40			
5a	4.8	30	37	40			
73	6.9	30	44	43			
7b	15.0	28	42	32			
7c (cis)	13.8	41	38	44			
7c (trans)	2.9	42	40	41			
8b	>20	19	46	36			
10a	>20	12	17	18			
13a	10.0	34	35	31			
14a	9.5	20	27	26			

<sup>a</sup>For structures, see Table III. <sup>b</sup>See footnote b. Table I. <sup>c</sup>Disk containing ca. 30  $\mu$ g.

lis, and Sarcina lutea which was comparable to that of cephalothin. One explanation for the low potency against resistant staphylococcus might be that the extension of conjugation at the 3 position of these new compounds contributes to an extremely reactive  $\beta$ -lactam sensitive to penicillinase. Experiments (results courtesy of Dr. J. Turner and Ms. Lois Short) using isolated and purified staphylococcal penicillinase indicate that compounds 14a and 14b are not more susceptible to this enzyme than is cephalothin. Compounds 7a, 8a, and 13a are slightly more readily destroyed, and 7b, 8b, and 13b are considerably more sensitive to staphylococcal penase than cephalothin.

The in vitro gradient-plate activities of a series of 3-(substituted)vinylcephem derivatives against several gram-negative bacteria are given in Table III. There is an indication that the carbethoxy contributes superior (relative to carboxy) activity in the phenoxyacetyl (5), thiopheneacetyl (7), and phenylmalonoyl (14) series against Escherichia coli, Klebsiella pneumoniae, and Enterobacter aerogenes.

### Table III. Gram-Negative<sup>a</sup> Activity of 3-(Substituted)vinylcephems



Compound	R	х	Shig.	E. coli	К. рп.	Ent. aerog.	Sal. heid.	S. marces.	P. aerug.
Cephalothin			17.4	17.3	2.1	4.7	2.2	>200	>200
5a	$\mathbf{PhOCH}_{2}$	$CO_2Et$	16.4	17.9	7.6	16.3	20.3	>50	>50
5b	$PhOCH_2$	$CO_2H$	>50	>50	19.6	28.5	14.9	>50	>50
<b>5c</b> (cis)	$PhOCH_2$	CN	>100	>100	77.0	80.0	76.0	>200	>200
5c (trans)	$PhOCH_2$	CN	104	102	38.8	40.5	102	>200	>200
7a	$2-CH_2-C_4H_3S^d$	$CO_2Et$	2.6	3.8	5.3	3.3	4.7	> 200	>200
7b	$2-CH_2-C_4H_3S^d$	$CO_2H$	26.0	33.0	8.5	2.0	1.0	>200	>200
7c (cis)	$2-CH_2-C_4H_3S^d$	CN	>200	>200	184	76.5	65.7	>200	>200
7c (trans)	$2-CH_2-C_4H_3S^d$	CN	49.2	21.4	9.7	9.4	7.2	>200	>200
8a	PhCH(OH)	$CO_2Et$	0.6	2.0	8.5	0.9	1.0	46.8	>200
8b	PhCH(OH)	$CO_2H$	1.0	1.0	3.0	0.4	0.5	140	>200
10a	$PhCH(NH_2)$	$CO_2Et$	>200	>200	>200	>200	>200	>200	>200
(TFA salt)									
10b (TEA colt)	$PhCH(NH_2)$	CO <sub>2</sub> H	80	108	140	150	124	>200	>200
(IFA Salt)									
<b>11</b> a	0 ± NCH	$\mathbf{CO}_{2}\mathbf{Et}$	3.5	6.3	18.8	7.3	5.7	>200	>200
<b>1</b> 1b	0 * NCH	$CO_2H$	3.8	6.1	7.7	4.7	2.5	>200	>200
<b>12</b> a	NCH	$CO_2Et$	2.2	4.5	27.9	8.6	8.3	>200	>200
12b	N L NSN	$CO_2H$	6.6	7.4	8.6	7.8	7.9	>200	>200
13a	CH	CO <sub>2</sub> Et	7.9	18.0	12.2	8.6	7.7	>200	>200
13b	CH	CO <sub>2</sub> H	3.8	5.8	31.5	9.2	7.2	>200	>200
$N-Ac-7-ACA^{b}$	9	2	100	114	72.2	78.0	70.7	>200	>200
Carbenicillin			4.7	8.8	>200	44.2	1.5	1.6	26.0
Phenylmalonoyl- 7-ACA <sup>c</sup>			14.1	58.8	20.1	17.5	8.1	8.2	200
14a (disodium salt)	$PhCH(CO_2H)$	$\mathbf{CO}_{2}\mathbf{Et}$	1.0	6.3	2.5	3.0	0.8	0.6	42.2
14b (trisodium salt)	$PhCH(CO_2H)$	$CO_2H$	8.7	55.0	46.0	6.0	3.1	3.7	31.0

<sup>a</sup>See footnote c, Table I. <sup>o</sup>For preparation, see ref 16. <sup>o</sup>Prepared by acylating 7-ACA with *tert*-butylphenylmalonoyl chloride and removing the *tert*-butyl ester from the product with formic acid. <sup>d</sup>C<sub>4</sub>H<sub>3</sub>S = thienyl.

This trend does not hold in the series mandeloyl<sup>11</sup> (8), sydnoneacetyl<sup>11b</sup> (11), tetrazoleacetyl<sup>11b</sup> (12), and acetyl (13) where the data suggest that compounds with both 3-substituents have the same activity range. From the limited data (series 5 and 7), the cyanovinyl substituent does not seem to be a good contributor to antibacterial activity. Although not evident in the poorly active phenoxyacetyl pair 5c, the pair 7c suggests that *trans*-3-cyanovinyl imparts significantly better gram-negative activity than does the cis. The data in Table II imply the same trend as deduced from penicillin-resistant staphylococcus activity. Other derivatives of the 3-cyanovinyl series were not prepared. [We have observed a lack of reproducibility in the cyanovinylforming Wittig reaction. Initial experiments using (cyanomethylene)triphenylphosphorane prepared by us were successful. Subsequently, another lot of phosphorane prepared by us, as well as commercial material, failed to undergo the desired coupling.] Compounds **7a**, **8a**, and **8b** have activity (Table III) of the same order or slightly better than cephalothin.

The samples of sydnone derivatives 11a and 11b and the tetrazoleacetyl analogs 12a and 12b showed good gramnegative activity even though it was not possible to obtain completely pure material (see uv data in Table IV). The results are included because of the relevance of these 7-acylamino side chains in other cephem series.<sup>11b</sup>

The N-acetyl derivatives 13a and 13b showed surprisingly good activity compared to 7-acetamidocephalosporanic acid (N-acetyl-7-ACA) (shown in Table III), an indication (see below) that the structure-activity relationship of these

Table IV. 3-(Substituted)vinylcephem Derivatives

Compound	Uv, $\lambda \max$ , nm ( $\epsilon$ )	Formula	Analyses
5a	320 (24,400)	$C_{20}H_{20}N_2O_7S$	С, Н, N
5b	320 (20,000)	$C_{18}H_{16}N_2O_7S$	С, Н, N
<b>5c</b> (cis)	322 (15,500)	$C_{18}H_{15}N_3O_5S$	а
5c (trans)	320 (12,900)	$C_{18}H_{15}N_{3}O_{5}S$	а
7a	320 (20,000)	$C_{18}H_{18}N_2O_6$	С, Н, N
7b	317 (20,800)	$C_{16}H_{14}N_2O_6S_2$	С, Н, N
7c (cis)	323 (17,500)	$C_{16}H_{13}N_3O_4S_2$	a
7c (trans)	319 (12,000)	$C_{16}H_{13}N_3O_4S_2$	а
<b>8</b> a	320 (25,000)	$C_{20}H_{20}N_2O_7S$	С, Н, N
8b	315 (19,200)	$C_{18}H_{16}N_2O_7S$	С, Н, N
10a	320 (19,800)	$C_{20}H_{21}N_{3}O_{6}S$ •	b
	TFA salt	$CF_3CO_2H$	
10b	316 (15,200)	$C_{18}H_{17}N_{3}O_{6}S$ •	b
	TFA salt	$CF_3CO_2H$	
<b>11</b> a	313 (17,400)	$C_{16}H_{16}N_4O_8S$	С
11b	317 (13,800)	$C_{14}H_{12}N_4O_8S$	С
12a	317 (16,900)	$C_{15}H_{16}N_6O_6S$	С
12b	317 (11,000)	$C_{13}H_{12}N_6O_6S$	С
13a	321 (24,300)	$C_{14}H_{16}N_2O_6S$	С, Н, N
13b	317 (22,200)	$C_{12}H_{12}N_2O_6S$	С, Н, N
14a	319 (24,400)	$C_{21}H_{18}N_{2}O_{8}$ -	С, Н, М
14b	315 (20,200)	$C_{19}H_{13}N_2O_8-$ SNa <sub>3</sub>	d

<sup>a</sup>Isolated as gum. <sup>b</sup>See text. <sup>c</sup>Amorphous solid. <sup>a</sup>C: calcd, 45.79; found, 44.80. H: calcd, 2.63; found, 3.19. N: calcd, 5.62; found, 5.20.

new cephem nuclei diverges from that of 7-ACA. The results for the phenylglycyl series 10 were disappointing in view of the powerful gram-negative influence usually observed with this side chain.<sup>12</sup> However, experiments which followed the loss of uv absorption by 10a and 10b in solution indicated that these compounds have solution instability. Thus, decomposition may supercede bacterial inhibition during the incubation in agar.<sup>13</sup>

Phenylmalonyl derivatives 14a and 14b were also prepared. The phenylmalonoyl analog of 6-APA, carbenicillin, is well known to retain activity against Serratia marcescens and Pseudomonas aeruginosa, as indicated in Table III. The overwhelming majority of cephalosporins previously documented in the literature do not show activity against these two resistant gram-negative organisms.<sup>12</sup> Even phenylmalonoyl-7-ACA, as indicated in the table, has no antipseudomonas activity and only modest ability to inhibit serratia. In light of these facts, the activity against P. *aeruginosa* of 14a and 14b and against S. marcescens of 14a (and to a lesser extent, 14b) is noteworthy and reinforces the thesis that structure-activity relationships are not followed identically throughout all cephem nuclei.

Members of the 3-(substituted)vinylcephem series are able to protect mice from experimental infections (e.g., *Streptococcus pyogenes*). The details of the in vivo characteristics of important members of this series as well as a more extensive evaluation of their in vitro microbiological activity will be reported in a subsequent paper.

#### **Experimental Section**

Melting points were determined using a Kofler hot stage and are uncorrected. Uv spectra were run in EtOH or MeOH; ir spectra were taken in CHCl<sub>3</sub> or as a Nujol mull; and NMR spectra were determined on a Varian HA-60 or T-60 instrument in CDCl<sub>3</sub>, acetone- $d_6$ , or Me<sub>2</sub>SO- $d_6$ . All crystalline compounds were characterized by uv, ir, NMR, and elemental analyses (C, H, N). Unless stated otherwise these analyses were within ±0.4% of the theoretical value. All biologically active compounds appeared as one zone on a bioautograph of a paper chromatogram of 1  $\mu$ g of material.

3-(2'-Ethoxycarbonylvinyl)-7-phenoxyacetamido-3-

**cephem-4-carboxylic Acid (5a).** To a cooled solution of 2.180 g (5 mmol) of *tert*-butyl 3-hydroxymethyl-7-phenoxyacetamido-3-cephem-4-carboxylate 1-oxide<sup>14</sup> (1) in 200 ml of dry acetone was added 3.5 cc of Jones reagent (26.72 g of  $CrO_3$  in 23 cc of  $H_2SO_4$  diluted to 100 cc with  $H_2O$ ). After stirring for 5 min and quenching with *i*-PrOH, most of the acetone was removed under reduced pressure. EtOAc and saturated NaCl solution were added to the residue. The organic layer was washed twice with saturated NaHCO<sub>3</sub> solution and once with NaCl solution, dried over MgSO<sub>4</sub>, filtered and evaporated to give 2.15 g of crude sulfoxide aldehyde 2.

To a solution of 0.5 mmol of sulfoxide aldehyde 2 in 10 ml of dry  $C_6H_6$  was added 175 mg (1 equiv) of (carbethoxymethylene)triphenylphosphorane. After 48 hr at room temperature, the reaction mixture was evaporated to dryness, dissolved in 10 cc of 4:1 CH<sub>3</sub>CN-DMF, and cooled. To this solution were added 400 mg of powdered SnCl<sub>2</sub> and 0.45 ml of AcCl.<sup>15</sup> After 15 min in the cold and 2 hr at room temperature, the reaction mixture was evaporated to dryness, taken up in EtOAc and washed with saturated NaCl solution,  $3 \times \text{cold } 5\%$  HCl, NaHCO<sub>3</sub> solution, and NaCl solution, dried over MgSO<sub>4</sub>, filtered, and evaporated to give 175 mg of a yellow oil. This oil was purified by preparative TLC (elution with 3:1 C<sub>6</sub>H<sub>6</sub>-EtOAc) to give 103 mg of sulfide 4a. This material would not crystallize. The NMR spectrum showed vinyl doublets at  $\delta$  6.01 and 7.96 (J = 16 Hz).

A solution of 75 mg of ester 4a in 10 cc of 98–100% HCOOH was allowed to stand at room temperature for 1.5 hr. Evaporation of the formic acid and isolation of the acidic portion by extraction provided 55 mg of 5a, which could be crystallized from ether or ethanol: mp 193–196°.

3-(2'-Carboxyvinyl)-7-phenoxyacetamido-3-cephem-4-carboxylic Acid (5b). The sulfoxide aldehyde 2 was treated with (carbo-tert-butoxymethylene)triphenylphosphorane<sup>8</sup> and the sulfoxide moiety reduced similarly to the preparation of 4a. A 350-mg portion of the oily product, tert-butyl 3-(2'-tert-butoxycarbonylvinyl)-7-phenoxyacetamido-3-cephem-4-carboxylate (4b), after purification on column chromatography was dissolved in 20 cc of 98-100% HCOOH and allowed to stand at room temperature for 5 hr. The formic acid was evaporated under reduced pressure and the acidic portion of the residue separated by extraction to give 138 mg which could be crystallized from ether: mp 149-151°.

cis- and trans-3-(2'-Cyanovinyl)-7-phenoxyacetamido-3cephem-4-carboxylic Acid (5c). To a solution of 5.5 mmol of sulfoxide aldehyde 2 in 50 ml of 1:1 C<sub>6</sub>H<sub>6-i</sub>-PrOH was added 5.5 mmol of (cyanomethylene)triphenylphosphorane.7a After 36 hr, the reaction mixture was evaporated to dryness, redissolved in 30 cc of 1:1 DMF-CH<sub>3</sub>CN, and cooled, and 6 mmol of KI and 2 cc of AcCl were added. After 10 min in the cold and 50 min at room temperature, the mixture was concentrated under reduced pressure, taken up in EtOAc and washed with saturated NaCl solution, NaHCO3 solution, Na2S2O3 solution, and NaCl solution, dried over MgSO4, filtered, and evaporated. The resulting oil was separated via a combination of column chromatography on SiO<sub>2-15%</sub> H<sub>2</sub>O (elution with  $C_6H_6$  containing 1-3% EtOAc) and preparative TLC on Merck silica gel F-254 plates (elution with 3:1 C<sub>6</sub>H<sub>6</sub>-EtOAc) into the noncrystalline cis and trans isomers of tert-butyl 3-(2'cyanovinyl)-7-phenoxyacetamido-3-cephem-4-carboxylate (4c) which had similar ir spectra but different uv and NMR spectra (significant differences indicated). 4c (cis):  $\lambda_{max}$  317 nm ( $\epsilon$  16,800); vinyl H coupling constant = 12 Hz, C-2 H's quartet centered at  $\delta$ 4.01. 4c (trans):  $\lambda_{max}$  317 nm ( $\epsilon$  13,500); vinyl H coupling constant = 16 Hz, C-2 H's singlet at  $\delta$  3.55.

Each of the cis- and trans-tert-butyl esters 4c was in turn deesterified with 98% HCO<sub>2</sub>H for 1 hr at room temperature. After evaporation to dryness the acidic material was separated from each and obtained as a gum.

cis- and trans-3-( $2^{i}$ -Cyanovinyl)-7-thiopheneacetamido-3cephem-4-carboxylic Acid (7c). These 3-cyanovinyl derivatives were prepared in a manner similar to that used for preparation of phenoxyacetyl derivative 4c, starting from benzhydryl 3-hydroxymethyl-7-thiopheneacetamido-3-cephem-4-carboxylate 1-oxide (prepared from deacetylcephalothin by treatment with diphenyldiazomethane and then *m*-chloroperbenzoic acid). The acids were obtained as gums.

tert-Butyl 7-Amino-3-(2'-ethoxycarbonylvinyl-3-cephem-4-carboxylate Tosylate (6a)  $[(C_{23}H_{30}N_2O_8S_2) C, H, N]$ . To a solution of 1.75 mmol of oily tert-butyl 3-(2'-ethoxycarbonylvinyl)- 7-phenoxyacetamido-3-cephem-4-carboxylate (4a) in 50 ml of dry  $C_6H_6$  was added 1.4 equiv (196 mg) of dry pyridine and 1.4 equiv (511 mg) of PCl<sub>5</sub>. This mixture was heated at 58–60° under N<sub>2</sub> for 2 hr, evaporated to dryness, and dissolved in 50 ml of ice-cold MeOH. After 2 hr at room temperature, the MeOH was removed under reduced pressure and the residue dissolved in 50 ml of cold 1:1 THF-pH 4.5 buffer. After 30 min at room temperature, the mixture was concentrated under reduced pressure, EtOAc added, and the pH adjusted to 6.5 with solid NaHCO<sub>3</sub>. The organic layer was separated and washed twice with saturated NaCl solution, dried over MgSO<sub>4</sub>, filtered, and evaporated to a small volume. A solution of 330 mg of p-TsOH-H<sub>2</sub>O (1 equiv) in EtOAc was added. Upon cooling 571 mg of crystalline 6a precipitated. Recrystallization from *i*-PrOH provided material with mp 151–155°:  $\lambda_{max}$  321 nm ( $\epsilon$  21,800).

tert-Butyl 7-Amino-3-(2'-tert-butoxycarbonylvinyl)-3cephem-4-carboxylate Tosylate (6b)  $[(C_{25}H_{34}N_2O_8S_2) C, H, N]$ . Using a procedure similar to the one used in preparing tosylate 6a, tert-butyl 3-(2'-tert-butoxycarbonylvinyl)-7-phenoxyacetam-ido-3-cephem-4-carboxylate was converted to amino ester tosylate 6b: mp 166-168°;  $\lambda_{max}$  320 nm ( $\epsilon$  16,800).

**Preparation of 7a and 7b.** Acylation of nuclei **6a** and **6b** in turn with thiopheneacetyl chloride followed by deesterification provided **7a**, mp 191–193°, and **7b**, mp 139–141°, from ether.

3-Ethoxycarbonylvinyl-7-(2'-hydroxy)phenylacetamido-3cephem-4-carboxylic Acid (8a). The side chain of benzhydryl 7-acetamido-3-(ethoxycarbonyl)vinyl-3-cephem-4-carboxylate was cleaved using PCl<sub>5</sub> (1.3 equiv) and Et<sub>2</sub>NPh (1.75 equiv) in CH<sub>2</sub>Cl<sub>2</sub>. The crude amino ester was acylated in THF with o-formylmandeloyl chloride in the presence of NaHCO<sub>3</sub>. The reaction mixture was chromatographed on silica gel-15% H<sub>2</sub>O. The product, benzhydryl 3-(ethoxycarbonyl)vinyl-7-(2'-formyloxy)phenylacetamido-3cephem-4-carboxylate, was eluted with 2-4% EtOAc in C<sub>6</sub>H<sub>6</sub> and crystallized from Et<sub>2</sub>O: mp 196-199°;  $\lambda_{max}$  318 nm ( $\epsilon$  22,800).

A solution of 0.5 mmol (313 mg) of this material in 9 ml of  $HCO_2H-2$  ml of  $CH_2Cl_2$  was allowed to stand 1.75 hr at room temperature. The reaction mixture was evaporated to dryness, taken up in EtOAc, and extracted with NaHCO<sub>3</sub> solution. This extract was allowed to stand 4.5 hr at room temperature and then cooled and layered with EtOAc. The pH was adjusted to 3 by addition of 20% HCl, and the organic layer was separated, washed with NaCl solution, dried over MgSO<sub>4</sub>, filtered, and evaporated to give 257 mg of crude 8a which was crystallized from Et<sub>2</sub>O: mp 110-112°.

3-Carboxyvinyl-7-(2'-hydroxy)phenylacetamido-3-cephem-4-carboxylic Acid (8b). The side chain of benzhydryl 7-acetamido-3-(*tert*-butoxycarbonyl)vinyl-3-cephem-4-carboxylate was cleaved using PCl<sub>5</sub> and Et<sub>2</sub>NPh in CH<sub>2</sub>Cl<sub>2</sub>. The crude amino ester was acylated with o-formylmandeloyl chloride in THF in the presence of NaHCO<sub>3</sub>. Elution from silica gel-15% H<sub>2</sub>O with C<sub>6</sub>H<sub>6</sub>-2% EtOAc provides benzhydryl 3-(*tert*-butoxycarbonyl)vinyl-7-(2formyloxy)phenylacetamido-3-cephem-4-carboxylate which crystallized from Et<sub>2</sub>O-C<sub>6</sub>H<sub>12</sub>: mp 149-152°;  $\lambda_{max}$  313 nm ( $\epsilon$  21,800).

A solution of 0.5 mmol (327 mg) of this material in 10 ml of  $HCO_2H$  was allowed to stand 1.5 hr at room temperature. After evaporation to dryness, the residue was taken up in EtOAc and extracted with NaHCO<sub>3</sub> solution. This extract was allowed to stand 5.5 hr at room temperature, then cooled, layered with EtOAc, and adjusted to pH 2.8 with 20% HCl. The organic layer was separated, washed with NaCl solution, dried over MgSO<sub>4</sub>, filtered, and evaporated to give 195 mg of crude **8b**, which crystallized from EtOAc-actione imp 159-162°.

7-(2'-tert-Butoxycarbonylamino)phenylacettert-Butyl amido-3-(2"-ethoxycarbonylvinyl)-3-cephem-4-carboxylate (9a)  $[(C_{28}H_{37}N_3O_8S_1) C, H, N]$ . To a cooled solution of 0.3 mmol (160 mg) of tert-butyl 7-(2'-tert-butoxycarbonylamino)phenylacetamido-3-hydroxymethyl-3-cephem-4-carboxylate 1-oxide [prepared from tert-butyloxycarbonylcephaloglycine by (1) conversion to  $\Delta^2$ -tert-butyl ester [C. F. Murphy and R. E. Koehler, J. Org. Chem., 35, 2429 (1970)]; (2) deacetylation using B. subtilis esterase; and (3) sulfur oxidation with *m*-chloroperbenzoic acid] in 10 ml of acetone was added 0.3 ml of Jones reagent. After 1 min the reaction was poured into EtOAc and this mixture was washed with NaCl solution, NaHCO3 solution, and again with NaCl solution, dried over MgSO<sub>4</sub>, filtered, and evaporated to give 174 mg of crude sulfoxide aldehyde as a foam. This foam was dissolved in 20 ml of 1:1 *i*-PrOH-C<sub>6</sub>H<sub>6</sub> and 104 mg (1 equiv) of (carbethoxymethylene)triphenvlphosphorane was added. After 28 hr at room temperature, the reaction mixture was evaporated to dryness, dissolved in 8 ml of 1:1 CH<sub>3</sub>CN-DMF, and cooled. To the cooled solution was added 125 mg (0.75 mmol) of KI and 0.6 ml of AcCl. This mixture was stirred 5 min in the cold and 1.5 hr at room temperature, evaporated to dryness, taken up in EtOAc and washed with NaCl solution, NaHCO<sub>3</sub> solution, NaCl solution, dried over MgSO<sub>4</sub>, filtered, and evaporated to give 300 mg of crude product. Purification by preparative TLC provided 160 mg which crystallized from Et<sub>2</sub>O-cyclohexane to give pure 9a: mp 177-179°;  $\lambda_{max}$ 316 nm ( $\epsilon$  20,000).

tert-Butyl 7-(2'-tert-Butoxycarbonylamino)phenylacetamido-3-(2"-tert-butoxycarbonylvinyl)-3-cephem-4-carboxylate (9b) [( $C_{31}H_{41}N_3O_8S_1$ ) C, H, N]. Using a procedure similar to that for preparation of 9a, tert-butyl 7-(2'-tert-butoxycarbonylamino)phenylacetamido-3-hydroxymethyl-3-cephem-4-carboxylate 1-oxide was oxidized with Jones reagent. The resulting aldehyde was condensed with (tert-butoxycarbonylmethylene)triphenylphosphorane, and after sulfoxide reduction using KI and AcCl, the crude product was purified by chromatography. Crystallization from C<sub>6</sub>H<sub>6</sub> provided pure 9b: mp 197-198°;  $\lambda_{max}$  316 nm ( $\epsilon$  22,000). 7-(2'-Amino)phenylacetamido-3-(2"-carboxyvinyl)-3-

cephem-4-carboxylic Acid (10b). A solution of 25 mg of tertbutyl 7-(2'-tert-butoxycarbonylamino)phenylacetamido-3-(2''tert-butoxycarbonylvinyl)-3-cephem-4-carboxylate (9b) in 5 ml of 98-100% HCOOH was allowed to stand 1 hr at room temperature. After evaporation to dryness, the NMR was taken in TFA. After evaporation of the TFA, the residue showed a  $\beta$ -lactam in the ir and  $\lambda_{max}$  317 nm ( $\epsilon$  13,700). The bioautograph showed only one active zone against Sarcina lutea, more polar than cephalexin.

7-(2'-Amino)phenylacetamido-3-(2''-ethoxycarbonylvinyl)-3-cephem-4-carboxylic Acid (10a). This compound was prepared from 9a in a manner similar to that used for converting 9b to 10b.

3-Ethoxycarbonylvinyl-7-(2-sydnoneacetamido)-3-cephem-4-carboxylic Acid (11a). The amino ester nucleus 6a was acylated in THF with sydnoneacetyl chloride. The crude product was purified by column chromatography on SiO<sub>2</sub>-15% H<sub>2</sub>O. The benzhydryl ester of 11a was eluted with  $C_6H_6-25-50\%$  EtOAc and crystallized from CH<sub>2</sub>Cl<sub>2</sub>-Et<sub>2</sub>O: mp 208-209°;  $\lambda_{max}$  308 nm ( $\epsilon$ 15,700); NMR (CDCl<sub>3</sub> + Me<sub>2</sub>SO-d<sub>6</sub>) vinyl doublets at  $\delta$  6.07 and 7.83, sydnone H at  $\delta$  6.55, side-chain methylene at  $\delta$  5.03, and other absorption consistent with the assigned structure.

A solution of 208 mg of this benzhydryl ester in 20 cc of 98–100% formic acid was allowed to stand at room temperature for 45 min. After evaporation to dryness, the residue was extrated into NaHCO<sub>3</sub> solution from EtOAc and the product 11a was isolated by acidification with 20% HCl and extraction back into EtOAc and obtained as 128 mg of an amorphous solid: NMR (acetone- $d_6$  + CDCl<sub>3</sub>) vinyl doublets at  $\delta$  6.15 and 7.97, sydnone H at  $\delta$  6.77, as well as other absorption consistent with structure 11a. This material showed one zone, slightly faster moving than cephalothin on bioautograph vs. Bacillus subtilis.

3-Carboxyvinyl-7-(2-sydnoneacetamido)-3-cephem-4-carboxylic Acid (11b). The amino ester nucleus 6b was acylated in THF with sydnoneacetyl chloride. The crude product was chromatographed on silica gel-15% H<sub>2</sub>O; the desired material was eluted with C<sub>6</sub>H<sub>6</sub>-25-45% EtOAc. After a final purification via preparative TLC, crystals could be obtained from CH<sub>2</sub>Cl<sub>2</sub>-Et<sub>2</sub>O, mp 158-160°. Although this material did not analyze correctly, spectral data indicated the desired benzhydryl ester:  $\lambda_{max}$  307 ( $\epsilon$  11,700); NMR (CDCl<sub>3</sub>) vinyl doublets at  $\delta$  5.93 and 7.77, sydnone H at  $\delta$  6.5, *tert*-butyl singlet at  $\delta$  1.4, and other absorption consistent with the assigned structure.

A 300-mg portion of the above material was doubly deesterified using 98-100% formic acid for 1 hr and the acidic material separated by extraction. The product, 53 mg of an amorphous solid, had NMR (acetone- $d_6$ ) vinyl doublets at  $\delta$  6.17 and 7.97, sydnone H at  $\delta$  6.85, as well as other absorption characteristic of 11b. This material gave a singlet zone at the origin on bioautograph vs. *B.* subtilis under conditions where cephalothin moved up 60% of the paper.

**3-Ethoxycarbonylvinyl-7-[2-(1H-tetrazol-1-yl)acetamido]-3-cephem-4-carboxylic Acid (12a).** The amino ester nucleus 6a was acylated in THF with tetrazoleacetyl chloride using NaHCO<sub>3</sub> as base. The crude product was purified by column chromatography on silica gel-15% H<sub>2</sub>O; the product was eluted with 24-40% EtOAc in C<sub>6</sub>H<sub>6</sub>. The product crystallized from C<sub>6</sub>H<sub>6</sub>: mp 175-178°. Although elemental analysis was not satisfactory, spectral data confirmed structure 12a benzhydryl ester:  $\lambda_{max}$  317 nm ( $\epsilon$  17,500); ir bands at 5.65 and 5.90  $\mu$ ; NMR (CDCl<sub>3</sub>) 1.1 (t) and 4.16 (q) (ethyl), 3.3 (s, C<sub>2</sub>), 4.88 (d, C<sub>6</sub>), 5.2 (s, side-chain methylene), 5.78 (q, C<sub>7</sub>), 5.96 (d, vinyl H), 6.96 (s, benzhydrylmethine), 7.36 (diphenyl protons), 7.88 (d, vinyl H), 8.75 (s, tetrazole H), 9.11 (d, NH). A solution of 110 mg of the benzhydryl ester in 8 ml of 98–100% formic acid was allowed to stand at room temperature for 0.5 hr. After evaporation to dryness, the acidic portion was extracted from EtOAc solution with NaHCO<sub>3</sub> solution; these extracts were acidified and the product was extracted back into EtOAc. After drying, there was obtained 56 mg of 12a as an amorphous solid. The NMR spectrum (acetone- $d_6$ ) showed a tetrazole H at  $\delta$  9.13, vinyl doublets at  $\delta$  6.23 and 7.97, as well as other absorption consistent with the spectrum of 12a. This material showed one spot slightly slower moving than cephalothin on bioautograph vs. *B.* subtilis.

3-Carboxyvinyl-7-[2-(1H-tetrazol-1-yl)acetamido]-3-

cephem-4-carboxylic Acid (12b). The amino ester nucleus 6b was acylated in THF with tetrazoleacetyl chloride. After purification by column chromatography and preparative TLC the product was obtained as a gum:  $\lambda_{max}$  317 nm ( $\epsilon$  17,000); ir bands at 5.6 and 5.85  $\mu$ ; NMR (CDCl<sub>3</sub>) tetrazole H at  $\delta$  8.83, vinyl doublets at  $\delta$  5.93 and 7.77, a *tert*-butyl singlet at  $\delta$  1.4, and other absorption consistent with the desired benzhydryl ester.

A 400-mg portion of this material was doubly deesterified by treatment with 98–100% formic acid for 45 min. After separation of acidic material and digestion with hot ether, 75 mg of 12b was obtained as an amorphous solid: NMR (acetone- $d_6$ ) tetrazole H at  $\delta$ 9.1, vinyl doublets at  $\delta$  6.13 and 7.93, as well as other absorption consistent with structure 12b. On bioautograph vs. *B. subtilis*, this material showed one spot, at the origin, under conditions where cephalothin moved up about 50% of the paper.

7-Acetamido-3-ethoxycarbonylvinyl-3-cephem-4-carboxylic Acid (13a). Benzhydryl 7-acetamido-3-hydroxymethyl-3cephem-4-carboxylate (prepared by treating deacetyl-7-ACA with ketene<sup>16</sup> and then diphenyldiazomethane) was oxidized in acetone with Jones reagent. After separation of the crude aldehyde by extraction, it was treated in 1:1  $C_6H_6$ -*i*-PrOH with 1 equiv of (ethoxycarbonylmethylene)triphenylphosphorane for 24 hr. After evaporation to dryness, column chromatography of the residue on SiO<sub>2</sub>-15% H<sub>2</sub>O provided the pure benzhydryl ester of 13a (eluted with 10-15% EtOAc in  $C_6H_6$ ) which was crystallized from hexane-CHCl<sub>3</sub> or ether: mp 178-179°;  $\lambda_{max}$  317 nm ( $\epsilon$  22,800).

A 253-mg (0.5 mmol) portion of this benzhydryl ester was dissolved in 10 cc of 98–100%  $HCO_2H$ . After 30 min at room temperature, the reaction mixture was evaporated to dryness and the residue crystallized from EtOAc-acetone to give 118 mg of acid 13a, mp 197-203°.

7-Acetamido-3-carboxyvinyl-3-cephem-4-carboxylic Acid (13b). Benzhydryl 7-acetamido-3-formyl-3-cephem-4-carboxylate was treated with 1 equiv of (*tert*-butoxycarbonylmethylene)triphenylphosphorane for 2 hr at room temperature. After evaporation to dryness, the residue was chromatographed on SiO<sub>2</sub>-15% H<sub>2</sub>O. The desired benzhydryl 7-acetamido-3-*tert*-butoxycarbonyl-vinyl-3-cephem-4-carboxylate was eluted with 6-8% EtOAc in C<sub>6</sub>H<sub>6</sub> and crystallized from Et<sub>2</sub>O: mp 109-111°;  $\lambda_{max}$  317 nm ( $\epsilon$  22,200).

A 267-mg (0.5 mmol) sample of this benzhydryl ester was dissolved in 12 cc of 98–100%  $HCO_2H$ . After 45 min at room temperature, the reaction mixture was evaporated to dryness and the residue crystallized from EtOAc-acetone to give 59 mg of acid 13b, mp 173–181°.

tert-Butyl 7-(2'-tert-Butoxycarbonyl)phenylacetamido-3-(2"-ethoxycarbonylvinyl)-3-cephem-4-carboxylate (Di-tertbutyl Ester of 14a) [(C<sub>29</sub>H<sub>36</sub>N<sub>2</sub>O<sub>8</sub>S<sub>1</sub>) C, H, N]. To a cooled suspension of 1.050 g (2 mmol) of amino ester tosylate 6a and 5 mmol of NaHCO<sub>3</sub> in 30 ml of dry acetone was added ca. 4 mol of tertbutylphenylmalonoyl chloride (prepared by treating 4 mmol of the corresponding acid in C<sub>6</sub>H<sub>6</sub> with 2 cc of oxalyl chloride and trace of DMF for 0.5 hr). After 15 min in the cold and 1.5 hr at room temperature, the reaction mixture was recooled and quenched by addition of H<sub>2</sub>O. After concentration under reduced pressure, the residue was taken up in EtOAc and washed with NaHCO<sub>3</sub> solution and saturated NaCl solution. After drying over MgSO<sub>4</sub>, filtration, and evaporation, 1.34 g of a pale green foam was obtained, which crystallized from Et<sub>2</sub>O (500 mg): mp 162-165°;  $\lambda_{max}$  317 nm ( $\epsilon$ 24,100).

7-(2'-Carboxy)phenylacetamido-3-(2"-ethoxycarbonylvinyl)-3-cephem-4-carboxylic Acid Disodium Salt (14a). A solution of 114 mg (0.2 mmol) of tert-butyl 7-(2'-tert-butoxycarbonyl)phenylacetamido-3-(2"-ethoxycarbonylvinyl)-3-cephem-4-carboxylate in 8 cc of 98-100% HCO<sub>2</sub>H was allowed to stand at room temperature for 1 hr. After evaporation to dryness, the residue was purged with EtOAc and then taken up in 10 cc of EtOH-5 cc of MeOH. A solution of 0.4 mmol of sodium 2-ethylhexanoate in EtOH was added, followed by 5 cc of *i*-PrOH. Concentration and cooling produced 66 mg of a slightly yellow solid, **14a**.

tert-Butyl 7-(2'-tert-Butoxycarbonyl)phenylacetamido-3-(2"-tert-butoxycarbonylvinyl)-3-cephem-4-carboxylate (Tritert-butyl Ester of 14b)  $[(C_{31}H_{40}N_2O_8S_1) C, H, N]$ . Using a procedure similar to that for preparation of the di-tert-butyl ester of 14a, amino ester tosylate 6b was acylated with tert-butylphenylmalonoyl chloride. The oily product was chromatographed over silica gel-15% H<sub>2</sub>O. The tri-tert-butyl ester was eluted with C<sub>6</sub>H<sub>6</sub>-2% EtOAc and crystallized from Et<sub>2</sub>O in the cold: mp 168-170°;  $\lambda_{max}$ 317 nm ( $\epsilon$  23,600).

7-(2'-Carboxy)phenylacetamido-3-(2"-carboxyvinyl)-3cephem-4-carboxylic Acid Trisodium Salt (14b). A solution of 120 mg (0.2 mmol) of *tert*-butyl 7-(2'-*tert*-butoxycarbonyl)phenylacetamido-3-(2"-*tert*-butoxycarbonylvinyl)-3-cephem-4-carboxylate in 5 cc of 98-100% HCO<sub>2</sub>H was allowed to stand at room temperature for 1 hr. After evaporation to dryness, the residue was purged with EtOAc and then taken up in 4 cc of EtOH-4 cc of MeOH. A solution of 0.6 mmol of sodium 2-ethylhexanoate in EtOH was added. A small amount of *i*-PrOH was added. Concentration and cooling precipitated 89 mg of 14b as a cream-colored solid.

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#### **References and Notes**

- A major portion of this work was included in a lecture by one of us at the Thirteenth National Medicinal Chemistry Symposium, Iowa City, Iowa, June 1972.
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  (b) After the completion of this work, a patent appeared [J. C. Clark, J. Kennedy, A. G. Long, and N. G. Weir, West German Patent 2103014 (1971)] which emphasized a different facet of 3-vinylcephem research. The only overlap between their work and ours was the analogs 7 and 10 in this paper. This material subsequently appeared in A. G. Long and N. G. Weir, U.S. Patent 3,769,277 (1973). Their reported results parallel ours.
- (3) For a summary of 3-(substituted)methylcephem derivatives and their synthesis and biological activity, see "Cephalosporins and Penicillins: Chemistry and Biology", E. H. Flynn, Ed., Academic Press, New York, N.Y., 1972, Chapters 4 and 12, respectively.
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## 9-Chloro-2,3-dihydro-5*H*-1,4-dioxepino[6,5-*b*]benzofuran, a Novel Antilipidemic Agent Structurally Related to Clofibrate<sup>†</sup>

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The synthesis and antilipidemic activity of 9-chloro-2,3-dihydro-5*H*-1,4-dioxepino[6,5-*b*]benzofuran (3), a novel enol lactone which is considerably more resistant to serum esterase hydrolysis than clofibrate (1), are discussed. Whereas both 3 and 1 reduced hypercholesterolemic and hypertriglyceridemic serum levels in the Triton WR-1339 induced hyperlipidemic Sprague-Dawley rat to normal, the hydrolysis product of 3, namely 5-chloro-3-(2'-hydroxyethoxy)-2benzofurancarboxylic acid (4), was found to be inactive. Further, 3 is comparable to the hydrolysis product of 1 when both were assessed for their ability to block norepinephrine (NE) induced lipolysis in vitro. 4 is inactive at comparable concentrations ( $5 \times 10^{-4}$ - $10^{-3} M$ ). The antilipidemic action of 3 and 1 may, in part, be due to their ability to block NE-induced lipolysis.

In previous reports from our laboratory we have considered the differential biological effects of certain benzodioxane, chroman, and dihydrobenzofuran analogs of clofibrate (1) on inhibition of lipolysis and cholesterol biosynthesis in vitro,<sup>1,2</sup> inhibition of lipoprotein lipase in vitro,<sup>3</sup> hypolipidemic activity in a Triton WR-1339 induced hyperlipidemic rat model,<sup>4,5</sup> and hepatic drug metabolism.<sup>6</sup> In all cases the ethyl esters of the various analogs were employed for biological studies in rats since we were interested in assessing new compounds synthesized relative to 1 which is administered as an ethyl ester. For studies in vitro, we investigated the corresponding free carboxylic acids since 1 and related ester analogs are known to undergo rapid hydrolysis by serum esterases and the carboxylic acids are presumed to be the active antilipidemic agents.<sup>7-10</sup>

In this article we describe the synthesis and antilipidemic activity of 9-chloro-2,3-dihydro-5H-1,4-dioxepino[6,5b|benzofuran (3), a novel enol lactone, which possesses a conformationally constrained ethyl group and is considerably more resistant to serum esterase hydrolysis. Tricyclic enol lactone 3 may be visualized as a cyclic analog of dihydrobenzofuran 2 where the  $\beta$ -carbon of the ethyl function is covalently bonded to the benzofuran ring at position 3 through an enol ether linkage. Dihydrobenzofuran 2, which only exhibits cholesterol lowering activity,<sup>4</sup> in turn, represents a molecular modification of 1, an analog which decreases to normal concentrations both cholesterol and triglycerides in the hyperlipidemic rat model.<sup>4</sup> The antilipidemic activity of 3 and its hydrolysis product 4 are discussed in light of their antilipolytic properties in vitro and compared to the biological activity of 1 and 2 and their corresponding hydrolysis products.



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Chemistry. The tetrahydropyranyl (THP) protected derivative of  $\beta$ -bromoethanol (5), namely 7, was prepared in 90% yield by condensation of 5 with dihydropyran (6) in the presence of a catalytic amount of p-TsOH and served as the source of the  $\beta$ -hydroxyethyl side chain of 4. Starting ethyl-5-chloro-2-carbethoxy-3(2H)-benzofuranone (9)<sup>11,12</sup> was prepared in 88% yield by Dieckmann condensation of ethyl 4-chloro-2-carbethoxyphenoxyacetate  $(8)^{13}$  with NaOEt in dry benzene.<sup>14</sup> The yield reported here is greater than the one reported by Schroeder and coworkers<sup>12</sup> owing to a longer reflux time. Reaction of anion 10 generated from 9 using NaH in dry diglyme with 7 for 5 hr at 150° afforded 11 as part of an uncharacterized mixture of products (GLC, see the Experimental Section). Hydrolysis of the mixture containing 11 in refluxing 10% ethanolic KOH for 1 hr, followed by cooling, acidification with 25% H<sub>2</sub>SO<sub>4</sub>, and THP protecting group removal under reflux for 10 min, afforded 5-chloro-3-(2'-hydroxyethoxy)-2-benzofurancarboxylic acid (4) in 52% yield based on starting 9. Hydroxy acid 4 was converted to the desired enol lactone 3 in 90% yield by refluxing in benzene containing a catalytic amount of p-TsOH.

3(2H)-Benzofuranone 9 does not form a 2,4-dinitrophenylhydrazone derivative under the mild conditions described by Pasto and Johnson;<sup>15</sup> however, after refluxing for 4 hr in concentrated HCl containing 2,4-DNPH the hydrazone formed in 40% yield. Keto derivatives are difficult to obtain since 9 exists in equilibrium with its aromatic enol form [ir (CHCl<sub>3</sub>) C=O stretching at 1670 and 1730 cm<sup>-1</sup>; OH stretching at 3350 cm<sup>-1</sup>]. Therefore, we anticipated 10 to be predominantly resonance stabilized as the  $\pi$ -excessive heteroaromatic oxygen anion; O-alkylation by 7 was expected to predominate. In fact, we were unable to isolate any C-alkylated product under a variety of reaction conditions. O-Alkylation was confirmed by the observation that enol lactone 3 failed to give a 2,4-dinitrophenylhydrazone derivative. Further, 3 showed only one C=O stretching

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