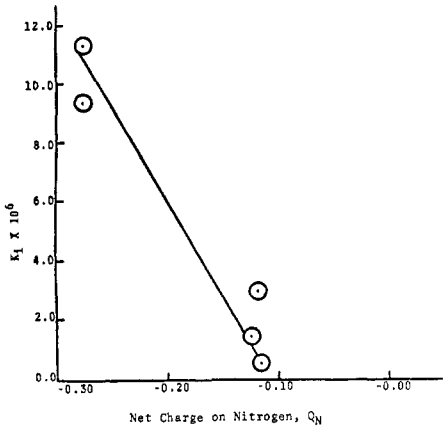


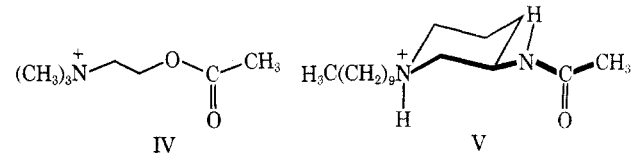
Figure 1.—Butyrylcholinesterase inhibition of some 3-substituted-1-decylpiperidines *vs.* net charge on the N of the substituent group. (Data points included are those for the compds for which K_i values have been determined, *i.e.*, **1–5**, Table II.)

were done on the nonprotonated species, however, to see if protonation of the piperidine nitrogen was "felt" by the substituent atoms at the 3 position of the piperidine ring. Using parameter values for a protonated piperidine nitrogen instead of a tertiary N did not change the charge densities on the atoms attached at the 3 position.

An explanation that has been proposed by Bergmann, *et al.*, for the cholinesterase inhibition of compds containing the RCO function is "that the inhibition is related to the effect of the substituting (R) group upon the electrophilic character of the carbonyl carbon."[10] With this in mind one would expect that an increase in the activity of the compds of series I, II, and III (**1–5**, Table II) would be reflected in an increase in the positive value for the net charge on the carbonyl C. This does not seem to be the case, however, as can be seen in Table II. Although the most active compd does have the most positive value as anticipated, the least active compds do not have the smallest positive charge on the carbonyl C. Thus, it would seem that while the electrophilic character of the carbonyl C is important for BuChE inhibition as illustrated by the most active compd (**2**, Table II), its contribution to BuChE inhibition is modified by the alkyl groups of the carboxamide function as seen in **3**, **4**, and **5**.

If one examines the total charge on the carbonyl O, Q_O, of **1–5** in Table II, it can be seen that the most active compd has the greatest negative charge. The total charge on the carbonyl O for the other compds has such small variation, however, that no conclusion can be drawn concerning a relationship between the total charge on the carbonyl O and activity.

Purcell has reported that, for a series of 1-decyl-3-[(*N*-alkyl)- and 1-decyl-3-[(*N*,*N*-dialkyl)substituted carbamoyl]piperidines, the BuChE inhibitory activity increased as the amide N became more positive.[11] The activity for the acetamide, urea, and substituted amides (**1–5**, Table II) increases as the N in the respective moieties (dimethyl-substituted N for **2**) becomes more positive (Figure 1). It is interesting to note that, whereas a part of the acetamide V shown by darker bonds is isosteric with the choline ester, acetylcholine (IV), and would thus be expected to "fit" the active site better than those compds which do not have the



ACh "backbone," it is less active than 2 of the carboxamide compds (**3** and **5**, Table II) in which the number of atoms separating the cationic N and the CO group is less than in the choline esters. This points out the dynamic nature of the interaction of inhibitor and enzyme; factors other than the proper positioning of certain atoms which are believed to be active-site-directing centers must also be of vital importance. Also, it is the charge density on the dimethyl-substituted N of **2** that seems to correlate with activity (Figure 1); this N is situated differently than either the N of the acetamide or the carboxamides. That the charge density on the differently situated (*i.e.*, regarding the number of bonds between the N and the piperidinium N) nitrogens is related to activity indicates that electronic charge densities may affect the manner in which the enzyme and inhibitor molecules fit together so that the piperidinium nitrogens and the nitrogens examined in Table II have similar distances between them.

A comparison was made of BuChE inhibitory activities and amide N charge densities for the series of carboxamide derivatives (**3–9**, Table II) in an attempt to delineate further the role of electrostatic charges in BuChE inhibition. Calcns show that there is very little variation in the charge distribution of the $CONH_2$ function while there is considerable variation in the BuChE inhibitory potencies, thus serving to illustrate that the hydrophobic character of the alkyl groups on the $CONH_2$ function is the controlling factor in the BuChE inhibition of these compds. These results are in agreement with those of Purcell, *et al.*, who attribute a major part of the activity of **3–9**, Table II, to relative hydrophobicities of the molecules.[2b]

Acknowledgment.—The authors wish to thank Mrs. Ann McEachran and Mrs. Julia Latham of the University of Tennessee Computer Project for their assistance in operating the IBM 1620 computer and Dr. George E. Bass for his assistance in the calculations. Also, we would like to express our gratitude to Dr. J. G. Beasley for permitting us to include some of his unpublished data in Table II and for his helpful comments on the manuscript.

(10) F. Bergmann, I. B. Wilson, and D. Nachmansohn, *J. Biol. Chem.*, **186**, 693 (1950).
(11) W. P. Purcell, *J. Med. Chem.*, **9**, 294 (1966).

Chemistry of Cephalosporin Antibiotics. 25. 3-Cyanomethyl Cephem Nucleus

J. A. WEBBER* AND R. T. VASILEFF

The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46206

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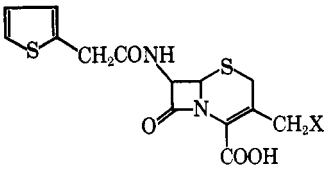
Numerous structural manipulations have been carried out at the 3 position of the cephem nucleus. Modifica-

TABLE I
ANTIBACTERIAL ACTIVITIES OF THIOPHENEACETYL DERIVATIVES



X	Resistant *S. aureus*[a]	Gram-negative[b] N-9	N-10	N-26	X-26	X-68	K-1	X-528
OAc	0.4	7.5	8.7	10.5	0.7	3.0	4.1	>50
H[c]	9.0	>50	>50	>50	6.4	>50	>50	>50
OCH_3[d]	0.4	>50	39.0	38.0	43.4	12.4	22.1	>50
SCH_3[e]	1.9	38.0	>50		16.8	18.3		>50
CN	2.4	30.0	22.5	27.0	5.2	8.8	8.1	>50

[a] MIC in μg/ml by gradient plate assay. Each figure is the avg value obtained using 3 penicillin-resistant, coagulase-positive *Staphylococcus aureus* strains. [b] MIC in μg/ml by gradient plate assay: N-9 = *Shigella* sp.; N-10 = *Escherichia coli;* N-26 = *E. coli;* X-26 = *Klebsiella pneumoniae;* X-68 = *Enterobacter aerogenes;* K-1 = *K. pneumoniae;* X-528 = *Pseudomonas* sp. [c] Ref 3; prepd by C. W. Ryan. [d] Ref 11. [e] Prepd by Dr. I. G. Wright, according to Belgian Patent 734,533 (1969).

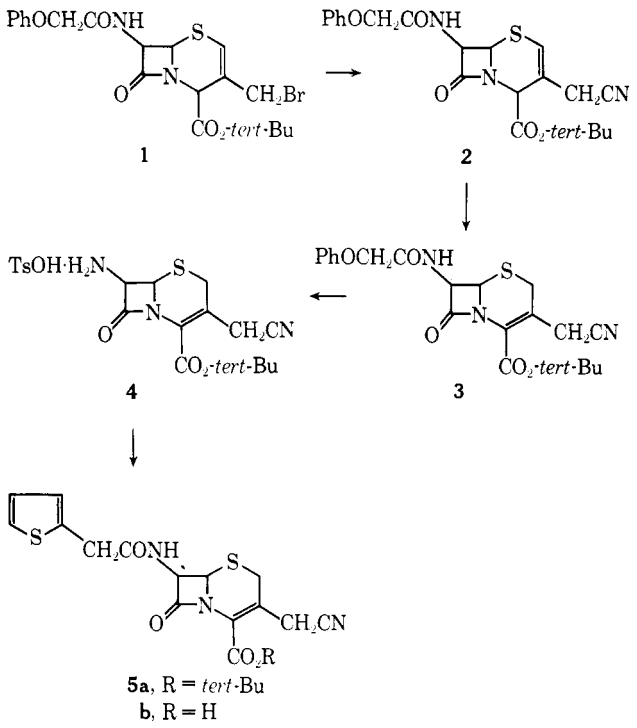
tions of the naturally occurring 3-acetoxymethyl function have resulted in direct replacement of AcO by S[1] and N[2] nucleophiles, hydrogenolytic cleavage[3] to a 3-Me moiety, and indirect replacement by S,[4] N,[4a,5] and O[5d,6] moieties.

There exist a few examples of cephalosporin derivatives in which the AcO group has been replaced by a C nucleophile. These were obtained *via* direct displacements by indole derivatives,[1a] resorcinol,[1a] and pyrroles[4] and indirect replacement by the enamine of cyclohexanone.[6a]

We wish to report the preparation of a 3-cyanomethyl cephem nucleus, the formal result of replacement of AcO by the C nucleophile, CN.[6b]

Starting material for our synthesis was the 3-bromomethyl-2-cephem derivative (**1**).[7,8] This allylic bromide undergoes acetate displacement[7] and also alcoholysis to give 3-alkoxymethyl cephem derivatives.[8] Attempts to displace Br from **1** by CN^-, ordinarily an excellent nucleophile, gave poor results using NaCN or KCN in numerous solvents; but the use of $Cu_2(CN)_2$, often used to replace aromatic halogens,[9] in a dipolar aprotic medium led to successful displacement. The best solvent was DMSO. Chromatography of the DMSO product provided crystalline 3-cyanomethyl-7-phenoxyacetamido-2-cephem-4-carboxylate ester (**2**). We feel that the unique success of $Cu_2(CN)_2$ in DMSO in this Br^- displacement results from an optimum compromise of solubility, nucleophilicity, and basicity which minimizes β-lactam destruction but still allows the desired displacement.

The 2-cephem derivative (**2**) was converted to its 3-cephem isomer (**3**) by oxidation and reduction at the S atom (see Experimental Section).[7,8,10]



5a, R = *tert*-Bu
b, R = H

Phenoxyacetyl side chain cleavage[11] of **3**, initiated by treatment with PCl_5, was performed successfully without extensive destruction of the CN moiety. Reacylation

(1) (a) J. D. Cocker, B. R. Cowley, J. S. G. Cox, S. Eardley, G. I. Gregory, J. K. Lazenby, A. G. Long, J. C. P. Sly, and G. A. Somerfield, *J. Chem. Soc.*, 5015 (1965); (b) E. Van Heyningen and C. N. Brown, *J. Med. Chem.*, **8**, 174 (1965).

(2) (a) C. W. Hale, G. G. F. Newton, and E. P. Abraham, *Biochem. J.*, **79**, 403 (1961); (b) J. L. Spencer, F. Y. Siu, E. H. Flynn, B. G. Jackson, M. V. Sigal, H. M. Higgins, R. R. Chauvette, S. L. Andrews, and D. E. Bloch, *Antimicrob. Ag. Chemother.*, 573 (1966); (c) J. Bradshaw, S. Eardley, and A. G. Long, *J. Chem. Soc. C*, 801 (1968).

(3) R. J. Stedman, K. Swered, and J. R. E. Hoover, *J. Med. Chem.*, **7**, 117 (1964).

(4) (a) J. S. G. Cox, H. Fazakerley, and J. D. Cocker, U. S. Patent 3,278,531 (1966); (b) Glaxo Lab. Ltd., Belgium Patent 734,532 (1969), and Glaxo Lab. Ltd., Belgium Patent 734,533 (1969).

(5) (a) E. P. Abraham, G. G. F. Newton, and C. W. Hale, U. S. Patent 3,226,384 (1965); (b) Glaxo Lab. Ltd., U. S. Patent 3,274,186 (1964); (c) Glaxo Lab. Ltd., Netherlands Patent 67,17107 (1968); (d) Glaxo Lab. Ltd., Belgium Patent 719,710 (1969).

(6) (a) Glaxo Lab. Ltd., Belgium Patent 719,711 (1969); (b) Eli Lilly, Netherlands Patent 69,02013 (1969).

(7) J. A. Webber, E. M. Van Heyningen, and R. T. Vasileff, *J. Amer. Chem. Soc.*, **91**, 5674 (1969).

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(10) G. V. Kaiser, R. D. G. Cooper, R. E. Koehler, C. F. Murphy, J. A. Webber, I. G. Wright, and E. M. Van Heyningen, *ibid.*, **35**, 2430 (1970).

(11) R. R. Chauvette, P. A. Pennington, C. W. Ryan, R. D. G. Cooper, F. L. Jose, I. G. Wright, E. M. Van Heyningen, and G. W. Huffman, *J. Org. Chem.*, **36**, 1259 (1971).

of the resulting amino ester nucleus, isolated as the tosylate salt (**4**), with thiopheneacetyl chloride provided the 3-cyanomethyl-7-thiopheneacetamido cephem ester (**5a**). Much decomposition occurred during ester cleavage of **3** or **5a** with acid. In the case of **5a**, however, some cephem acid material was isolated for antibacterial testing. The decomposition observed may result from carboxyl cyclization with the cyano moiety. The resulting iminolactone might then polymerize or otherwise lead to intractable material.

Table I provides gradient plate *in vitro* antibacterial activities for **5b** compared with other thiopheneacetamido cephem derivatives.

Experimental Section

Melting points were detd using a Mel-Temp app and are uncor. Uv spectra were detd in EtOH, ir spectra in $CHCl_3$ or as a mull. Nmr spectra were obtd using a Varian HA-60 spectrometer in $CDCl_3$, acetone-d_6, or DMSO-d_6. All cryst compds were characterized by ir, uv, nmr, and elemental anal. (C, H, N). Unless otherwise stated, anal. were within ±0.4% of the theor value.

***tert*-Butyl 3-Cyanomethyl-7-phenoxyacetamido-2-cephem-4-carboxylate (2).**—To a stirred, cooled soln contg 5.0 g (~10 mmoles) of bromide **1**, dissolved in 90 ml of DMSO and 30 ml of DMF, was added solid $Cu_2(CN)_2$ (896 mg, 10 mmoles). After being stirred with slow warming to 20° over 3 hr, 10 ml of cold 5% HCl contg 4.0 g of $FeCl_3 \cdot 6H_2O$ was added, and the mixt was stirred in the cold (0–5°) for 15 min. C_6H_6 and satd aq NaCl were added, and the sepd org layer was washed with satd aq NaCl, satd $NaHCO_3$, and satd NaCl and dried ($MgSO_4$ with decolorizing charcoal). Filtn and evapn of the C_6H_6 soln yielded 4.0 g of crude **2** which was purified by column chromatog on silica gel–15% H_2O. Compd **2** was eluted by 4% EtOAc in C_6H_6 and crystd from Et_2O, mp 117–120°.

***tert*-Butyl 3-Cyanomethyl-7-phenoxyacetamido-3-cephem-4-carboxylate (3).**—To a stirred, cooled soln contg 1.3 g (3 mmoles) of **2** dissolved in 40 ml of CH_2Cl_2 and 200 ml of *i*-PrOH was added dropwise 615 mg (3 mmoles) of *m*-$ClC_6H_4CO_3H$ (85%) dissolved in 100 ml of *i*-PrOH and 100 ml of CH_2Cl_2. The mixt was stirred for 4 hr and allowed to warm slowly to room temp before being evapd to dryness. The residue was dissolved in 12 ml of 3:1 CH_3CN–DMF, and cooled in an ice bath before 1.3 g of $SnCl_2$ (anhyd) and 5 ml of AcCl were added. After standing 50 min in the cold and 45 min at room temp, the reaction mixt was evapd to dryness, and then was dissolved in C_6H_6; this soln was washed with cold 5% HCl, satd $NaHCO_3$, and satd NaCl, then dried ($MgSO_4$), and evapd to give 1.7 g of crude **3** as an oil that was purified by column chromatog. The desired material, eluted by 4–8% EtOAc in C_6H_6, did not crystallize, but was characterized by spectral data.

***tert*-Butyl 7-Amino-3-cyanomethyl-3-cephem-4-carboxylate Tosylate (4).**—To a stirred soln contg 429 mg (1 mmole) of **3** dissolved in 20 ml of dry C_6H_6 was added 118 mg (1.5 equiv) of dry pyridine in 5 ml of dry C_6H_6; immediately following, 132 mg (1.5 equiv) of PCl_5 was added. After heating at 57° for 2 hr, the reaction mixt was cooled at room temp, evapd to dryness, and dissolved in 40 ml of cold MeOH. This soln was allowed to stand at room temp for 16 hr and then was evapd to dryness. To the residue was added 20 ml of THF and, after cooling, 20 ml of pH 4.5 buffer. After standing 20 min at room temp, THF was removed *in vacuo*, EtOAc was added to the residue, and the pH was adjusted to 6.5 by addn of $NaHCO_3$. The org layer was dried ($MgSO_4$) and evapd to give an oil. The cryst tosylate **4** mp 180–182°, was obtd by mixing EtOAc solns of the amine and TsOH.

***tert*-Butyl 3-Cyanomethyl-7-thiopheneacetamido-3-cephem-4-carboxylate (5a).**—To a stirred, cooled soln contg 467 mg (1.0 mmoles) of **4** suspended in 30 ml of Me_2CO was added 420 mg (5 mmoles) of solid $NaHCO_3$, followed by 482 mg (3 mmoles) of thiopheneacetyl chloride. The reaction mixt was stirred in the cold for 1 hr and at room temp for 3 hr; the Me_2CO was removed *in vacuo*, and the residue was dissolved in C_6H_6. This soln was washed with cold 5% HCl, satd $NaHCO_3$, and satd NaCl, and was dried ($MgSO_4$), evapd, and the residue was crystd from CCl_4 to give 418 mg, mp 164–166°.

3-Cyanomethyl-7-thiopheneacetamido-3-cephem-4-carboxylic acid (5b).—A soln of 455 mg of ester **5a** in 40 ml of 98–100% HCO_2H was stirred under N_2 for 2.5 hr at room temp. The HCO_2H was removed *in vacuo*, and the residue was dissolved in EtOAc–$NaHCO_3$. The layers were sepd, and a second extn was performed with a $NaHCO_3$ soln. The aq exts were cooled, layered with EtOAc, and adjusted to pH 2.8 with 20% HCl. The org layer was washed with NaCl, dried ($MgSO_4$), and evapd to give 234 mg of a golden foam. Crystn from Et_2O gave 97 mg of acid **5b**, mp 114–117°, characterized by spectral methods: uv, 268 mμ (ε 5400); ir (mull), C=O abs at 5.57, 5.80, and 6.03 μ. This material showed only 1 spot which was slightly faster moving than cephalothin on bioautogram (against *Bacillus subtilis*) in MEK–H_2O (98:2).

Synthesis and Pharmacological Activity of Dialkylaminoalkyl Esters of Benzilic Acids Containing Fluorine or Trifluoromethyl Groups

I. LALEZARI,* M. HATEFI,

Department of Chemistry, Faculty of Pharmacy

M. A. KHOYI, N. GUITI, AND F. ABTAHI

Department of Experimental Medicine and Pharmacology, Faculty of Medicine, University of Tehran, Iran

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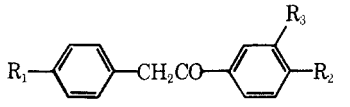
Continuing our studies on the synthesis of new potent local anesthetics,[1] and prompted by previous work on

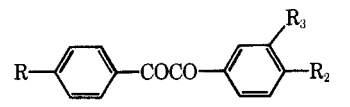
TABLE I



No.	R_1	R_2	R_3	Yield, %	Mp, °C	Bp (mm), °C	Method	Formula[a]
Ia	F	H	H	74	110–111[b]	152–155 (5)	A	$C_{14}H_{11}FO$
Ib	F	F	H	44	95–96	178–180 (15)[c]	A	$C_{14}H_{10}F_2O$
Ic	H	H	CF_3	75		166–168 (6.5)	B	$C_{15}H_{11}F_3O$
Id	F	H	CF_3	72		198–200 (753)	B	$C_{15}H_{10}F_4O$

[a] All compds were analyzed for C, H, and the anal. values obtained were within ±0.4% of the calcd figures. All compds were also subjected to ir and nmr spectroscopy and showed the expected absorptions. [b] A. Fisher, B. A. Grigor, J. Packer, and J. Vaughan, *J. Amer. Chem. Soc.*, **83**, 4208 (1961), report mp 111°. [c] W. Funasaka, T. Ando, H. Ozahi, and K. Murakami, *Yuki Gosei Kagaku Kyokai Shi*, **17**, 334 (1959) [*Chem. Abstr.*, **53**, 17970 (1959)], report mp 96–97°, bp 178–180° (15 mm). [d] N. Sharghi and I. Lalezari, *J. Chem. Eng. Data*, **10**, 196 (1965), report bp 166–168° (5.5 mm).

TABLE II



No.	R_1	R_2	R_3	Yield, %	Mp, °C	Formula[a]
IIa	F	H	H	65	58–60[b]	$C_{14}H_9FO_2$
IIb	F	F	H	84	121–122[c]	$C_{14}H_8F_2O_2$
IIc	H	H	CF_3	72	65	$C_{15}H_9F_3O_2$
IId	F	H	CF_3	68	68–69	$C_{15}H_8F_4O_2$

[a] See footnote *a*, Table I. [b] G. G. Smith and O. Larson, *J. Amer. Chem. Soc.*, **82**, 104 (1960), report mp 62–63°. [c] Smith and Larson[b] report mp 121.5–122.5°.

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