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

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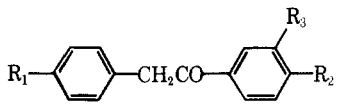
Received November 19, 1970

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

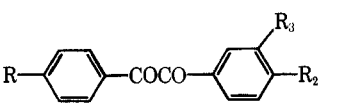
TABLE I



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°.

(1) N. Sharghi, I. Lalezari, G. Niloofari, and H. Golgolab, *J. Med. Chem.*, **12**, 696 (1969).

SCHEME I

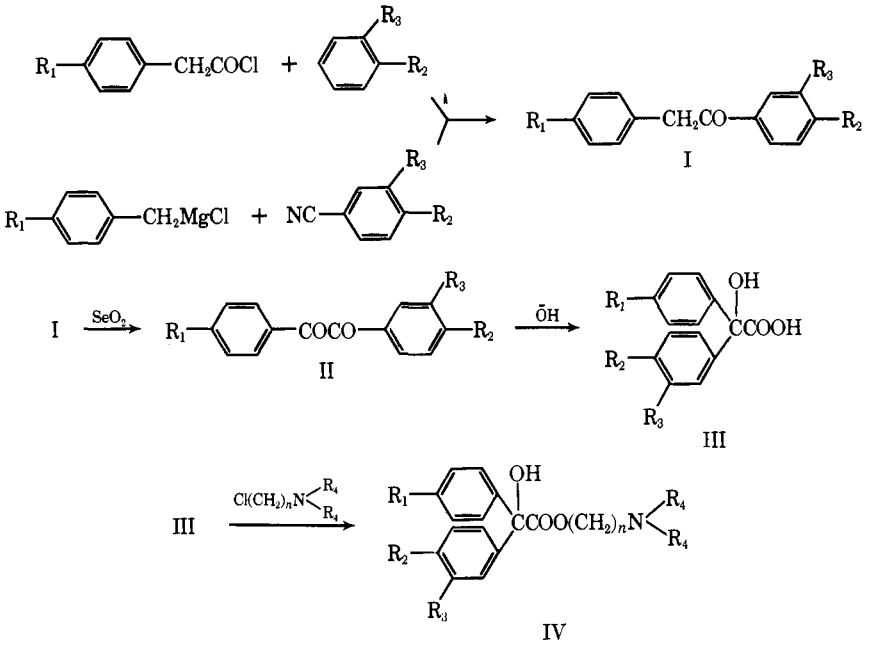
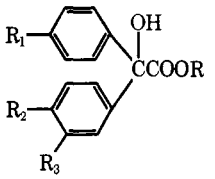


TABLE III



No.	R_1	R_2	R_3	R	Yield, %	Mp, °C	Formula[a]
IIIa	F	H	H	H	61[b]	116	$C_{14}H_{11}FO_3$
IIIb	F	F	H	H	69	143	$C_{14}H_{10}F_2O_3$
IIIc	H	H	CF_3	H	65	102	$C_{15}H_{11}F_3O_3$
IIId	F	H	CF_3	H	72	122	$C_{15}H_{10}F_4O_3$
IVa	F	H	H	$(CH_2)_2N(CH_3)_2 \cdot HCl$	54	192	$C_{18}H_{21}ClFNO_3$
IVb	F	F	H	$(CH_2)_2N(CH_3)_2 \cdot HCl$	51	188	$C_{18}H_{20}ClF_2NO_3$
IVc	F	H	H	$(CH_2)_3N(CH_3)_2 \cdot HCl$	64	184	$C_{19}H_{23}ClFNO_3$
IVd	F	F	H	$(CH_2)_3N(CH_3)_2 \cdot HCl$	62	178	$C_{19}H_{22}ClF_2NO_3$
IVe	H	H	CF_3	$(CH_2)_2N(CH_3)_2 \cdot HCl$	66	177	$C_{19}H_{21}ClF_3NO_3$
IVf	F	H	H	$(CH_2)_2N(C_2H_5)_2 \cdot HCl$	64	170	$C_{20}H_{25}ClFNO_3$
IVg	F	F	H	$(CH_2)_2N(C_2H_5)_2 \cdot HCl$	52	182	$C_{20}H_{24}ClF_2NO_3$
IVh	F	H	H	$(CH_2)_2N(CH_2)_5 \cdot HCl$	56	170	$C_{21}H_{25}ClFNO_3$
IVi	F	F	H	$(CH_2)_2N(CH_2)_5 \cdot HCl$	60	181	$C_{21}H_{24}ClF_2NO_3$
IVj	H	H	CF_3	$(CH_2)_2N(C_2H_5)_2 \cdot HCl$	50	165	$C_{21}H_{25}ClF_3NO_3$
IVk	F	H	CF_3	$(CH_2)_2N(C_2H_5)_2 \cdot HCl$	52	158	$C_{21}H_{24}ClF_4NO_3$
IVl	F	H	CF_3	$(CH_2)_2N(CH_2)_5 \cdot HCl$	53	165	$C_{22}H_{24}ClF_4NO_3$
IVm	H	H	CF_3	$(CH_2)_2N(CH_2)_5 \cdot HCl$	80	159	$C_{22}H_{25}ClF_3NO_3$
IVn	F	H	H	$(CH_2)_2N(CH_2C_6H_5)_2 \cdot HCl$	60	186	$C_{30}H_{29}ClFNO_3$
IVo	F	F	H	$(CH_2)_2N(CH_2C_6H_5)_2 \cdot HCl$	56	172	$C_{30}H_{28}ClF_2NO_3$
IVp	H	H	CF_3	$(CH_2)_2N(CH_2C_6H_5)_2 \cdot HCl$	72	169	$C_{31}H_{29}ClF_3NO_3$
IVq	F	H	CF_3	$(CH_2)_2N(CH_2C_6H_5)_2 \cdot HCl$	54	162	$C_{31}H_{28}ClF_4NO_3$
IVr	H	H	CF_3	$(CH_2)_3N(CH_3)_2 \cdot HCl$	65	140	$C_{20}H_{23}ClF_3NO_3$

[a] See footnote a Table I. [b] See footnote *b*, Table II, mp 113–114°.

organofluorine drugs, we have prepared the title compounds. Several dialkylaminoalkyl esters of fluorinated and trifluoromethylated benzilic acids have been prepared and subjected to pharmacological screening. Some of the compounds were found to be potent local anesthetics, and to have anticholinergic and antihistaminic activities.

The general synthesis is shown in Scheme I.

Pharmacological Evaluation.—Compds IVb, IVd, IVe, IVh, IVi, IVk, IVm, and IVr were screened for surface anesthetic, anticholinergic, and antihistaminic activity. The results are summarized in Table IV. These compds were injected intraspinally, in a concn of 0.5%, in rabbits. The duration of urethral areflexia[2]

(2) R. A. Turner, "Screening Methods in Pharmacology," Academic Press, New York, N. Y., 1965, p 268.

TABLE IV[a]

Compd	Concn, %	Rabbit cornea: Potency	Rabbit cornea: Duration, min	Guinea pig cornea: Potency	Guinea pig cornea: Duration, min	Guinea pig ileum: Dose, μg/ml	Guinea pig ileum: Anticholinergic	Guinea pig ileum: Antihistaminic
IVb	1	0	0	0	0	1	70	57
						10	100	100
IVd	1	0	0	0	0	1	5	10
						10	43	52
IVe	0.25	0.02 (0–0.04)	0–3	0.25 (0.17–0.33)	2–7	1	52	68
	0.50	0.72 (0.64–0.81)	12–18	0.88 (0.82–0.94)	12–24	10	98	100
	1	0.93 (0.88–0.98)	17–21	1.00	18–51			
IVh	1	0.45 (0.36–0.55)	4–17	0.82 (0.75–0.90)	0–36	1	55	85
						10	100	100
IVi	1	0.56 (0.47–0.66)	8–16	0.80 (0.73–0.88)	5–54	1	58	52
						10	96	100
IVk	0.25	0.05 (0–0.09)	0–2	0.33 (0.24–0.42)	2–11	1	15	27
	0.50	0.55 (0.45–0.64)	6–18	0.97 (0.94–1.00)	21–36	10	100	100
	1	1.00	21–33	1.00	36–96			
IVm	0.25	0.10 (0.04–0.16)	0–8	0.50 (0.40–0.60)	4–14	1	23	50
	0.50	0.82 (0.75–0.88)	13–21	0.99 (0.97–1.00)	18–42	10	97	100
	1	1.00	30–48	1.00	27–84			
IVr	0.25	0.98 (0.95–1.00)	26–39	0.48 (0.38–0.58)	4–17	1	25	10
	0.50	1.00	30–55	0.98 (0.95–1.00)	30–40	10	83	57
Benactyzine	0.25	0.40 (0.30–0.49)	5–16	0.39 (0.29–0.48)	5–11	0.1	100	21
	0.50	0.59 (0.50–0.69)	7–23	0.46 (0.37–0.56)	7–26	1	100	87
	1	0.98 (0.95–1.00)	19–35	0.99 (0.97–1.00)	23–40			
Cocaine	0.25	0.13 (0.08–0.18)	2–6	0.09 (0.04–0.15)	0–5			
	0.50	0.54 (0.47–0.62)	7–15	0.55 (0.45–0.64)	4–18			
	1	0.95 (0.92–0.98)	16–24	0.61 (0.52–0.70)	8–21			

[a] Surface anesthesia was tested according to the method of M. R. A. Chance and H. J. Lobstein, *J. Pharmacol. Exp. Ther.*, **82**, 203 (1944); and the anesthetic potency was calculated for the first 18 min, A. H. Campbell, J. A. Stasse, G. H. Lord, and J. E. Willson, *J. Pharm. Sci.*, **57**, 2045 (1968). A potency of 1.00 indicates an onset of anesthesia in 1 min and a duration of at least 18 min. Reduction of contractions (%) against acetylcholine, 0.1 μg/ml, and histamine dihydrochloride, 0.01 μg/ml. Assay was carried out on isolated organs (ref 2, p 43). The test compounds were added to the bath 30–60 sec before the agonists.

was 3, 0, 19, 15, 16, 34, 20, and 23 min, resp. Benactyzine·HCl and procaine·HCl, in the same concn, caused 22 and 5 min of areflexia, resp. In guinea pigs, IVe, IVk, IVm, and IVr caused conjunctival congestion in the first hr and slight opalescence of the cornea was present 48 hr after instillation. The LD_{50} of IVm in mice, estimated by the moving average method[3] was 121 (85–172) mg/kg. Substitution in the Ph rings of benzilic acid β-diethylaminoethyl ester·HCl (benactyzine·HCl) resulted in decreased anticholinergic activity but did not affect the antihistaminic activity. The antihistaminic activity was decreased when the dialkylaminoethyl chain was replaced by dialkylaminopropyl. CF_3 substituted in the Ph rings increase the surface anesthetic activity. Compds bearing Et_2N or piperidino groups, compared with those having Me_2N group, were found to be more potent surface anesthetics.

Experimental Section[4]

3-Trifluoromethylphenyl-4′-fluorobenzyl Ketone (Id.)—*m*-Trifluoromethylbenzonitrile (20.5 g) (0.12 mole) in 48 ml of dry Et_2O was added dropwise to a Grignard reagent prepared from 22 g (0.15 mole) of *p*-fluorobenzyl chloride and 3.9 g (0.162 g-atom) of Mg. The reaction mixt was stirred, first at room temp and then on a steam bath for 3 hr, and decompd with ice and HCl. The ketone was extd with Et_2O, washed, dried, and distd after removal of the solvent.

Compd Ic was prepared similarly. Ia and Ib were obtd by the method described in refs given in Table I, footnotes *b–d*.

3-Trifluoromethyl-4′-fluorobenzil (IId).—SeO_2 (4.4 g, 0.04 mole) was dissolved in 50 ml of glacial AcOH. To the hot soln was added 11.2 g (0.04 mole) of Id and the mixt was refluxed for 3 hr. The Se ppt was filtered off and the soln was dild with H_2O. After cooling, the crystals were collected and recrystd from dil EtOH. The other compds II were prepd similarly.

3-Trifluoromethyl-4′-fluorobenzilic Acid (IIId).—To a soln prepd from 25 g of KOH and 100 ml of 50% EtOH was added 29.6 g of IId and the mixt was refluxed for 3 hr and concd on a steam bath. The residue was dild with H_2O and extd with Et_2O to remove the impurities. The clear H_2O soln was decolorized by charcoal, filtered, and acidified. The oily ppt was extd with Et_2O, and the solvent was evapd. The substituted benzilic acid was crystd slowly and was recrystd from dil EtOH. The other compds III were obtained similarly.

Dialkylaminoalkyl Esters (IV).—The appropriate benzilic acid (0.05 mole) and dialkylaminoalkyl chloride (0.05 mole) in 15 ml of dry *i*-PrOH was refluxed for 24 hr and the solvent was removed under reduced pressure. The residue was dissolved in 20 ml of H_2O, made alk with concd K_2CO_3 soln and extd with Et_2O. The Et_2O ext was dried ($MgSO_4$) and filtered. Dry HCl was bubbled into the resulting soln until the ppt was complete (normally the mixt was stored 1 day in the ice box to complete the crystn). The esters were recrystd from EtOH.

Acknowledgment.—We are grateful to Dr. M. L. Smith of Central Treaty Organization for providing essential materials for this research program and to Mrs. A. Ramazani and Miss S. Levtov for technical assistance.

(3) C. S. Weil, *Biometrics*, **8**, 249 (1952).

(4) Melting points were taken on a Kofler hot stage microscope. The ir spectra were detd with a Leitz Model III spectrograph. Nmr spectra were obtd on a Varian A60A instrument.