New Compounds: Synthesis of Carboxymethyl Carbodithioates

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Abstract □ The synthesis and characterization of some new carboxymethyl carbodithioates are reported.

Keyphrases □ Carboxymethyl carbodithioates—synthesized from 1-thioacylpiperidines, NMR spectra, TLC separation □ 1-Thioacylpiperidines—used in synthesis of carboxymethyl carbodithioates

Carboxymethyl carbodithioates (III) are valuable thioacylating agents for amines, amino acids, hydrazines, and other related compounds. Some of the resulting products and the derived metal complexes and heterocycles exert many biological actions, ranging from hypnotic, analgesic, and anesthetic activities to fungicidal, bactericidal, and tuberculostatic activities (1).

Thioacylation of thiols with carboxymethyl carbodithioates is also rapid and has been used for preparing various new dithioesters (2). By the polycondensation of dicarboxymethyl dicarbodithioates with diamines and dithiols, novel polymers containing thiocarbonyl groups were prepared recently (3). Several new carboxymethyl carbodithioates (Table I) now have been prepared according to Scheme I.

A 1-thioacylpiperidine (I) (Table II) reacts with bromoacetic acid to give the *S*-carboxymethylthioacylpiperidinium bromide (II) (Table II), which, on thiohydrolysis with hydrogen sulfide, is converted into the carboxymethyl carbodithioate (III). The 1-thioacylpiperidines (I) are obtained by the Willgerodt–Kindler reaction from the corresponding aldehydes or by thionation with phosphorus pentasulfide of the corresponding 1-acylpiperidines. Neither the long chain aliphatic carboxymethyl carbodithioates (III*a*–III*f*) nor carboxymethyl 4-nitrobenzenecarbodithioate (III*g*) reported here could be prepared by previous investigators (4); but with certain modifications in the preparative procedure, they are readily obtainable, as indicated in the *Experimental* section for II*g* and III*c*.

The long chain aliphatic carboxymethyl carbodithioates are stable, readily purified, crystalline solids;

Table II—Analytical Data for *S*-Carboxymethylthioacylpiperidinium Bromides (II)

Compound	Yield, %	Melting Point	Formula[a]
I*a*	83	Oil[b]	$C_{13}H_{25}NS$
I*b*	65	Oil[b]	$C_{15}H_{29}NS$
I*c*	77	37.5–39.5°[c]	$C_{17}H_{33}NS$
I*d*	63	46–48°[c]	$C_{19}H_{37}NS$
I*e*	74	54–55.5°[c]	$C_{21}H_{41}NS$
I*f*	79	61–62.5°[c]	$C_{23}H_{45}NS$
I*h*	79	147.5–148°[d]	$C_{18}H_{19}NS$
I*i*	93	76–78°[e]	$C_{12}H_{14}FNS$
I*j*	57	168.5–170°[f]	$C_{12}H_{15}NOS$
II*g*	98	167–169°	$C_{14}H_{17}BrN_2O_4S$
II*h*	70	154–154.5° dec.	$C_{20}H_{22}BrN_3O_2S$
II*i*	98	125–127° dec.	$C_{14}H_{17}BrFNO_2S$
II*j*	88	165–167°	$C_{14}H_{18}BrNO_3S$

[a] Compounds I*a*–I*j* showed correct M^+ peaks in the mass spectra. [b] Decomposed on distillation (0.1 mm Hg). [c] Crystallized from methanol. [d] Crystallized from ethanol. [e] Crystallized from petroleum ether (bp 40–60°). [f] Crystallized from methanol–water.

Table III—Analytical Data for *S*-Carboxymethyl Carbothioates (IV)

Compound	Melting Point	Color[a]	PMR[b], δ SCH_2	Formula[c]
IV*g*	156–157.5°[d]	C	3.97	$C_9H_7NO_5S$
IV*h*	167.5–168°[e]	O	3.92	$C_{15}H_{12}N_2O_3S$
IV*i*	105–106°[e]	C	3.90	$C_9H_7FO_3S$
IV*j*	138–143°[e]	C	3.90	$C_9H_8O_3S$
IV*k*	128.5–130.5°[e]	C	3.90	$C_{10}H_{10}O_4S$

[a] C = colorless, and O = orange. [b] Measured in acetone-d_6, except IV*g* which was measured in dimethylformamide-d_6 and IV*i* which was measured in deuterochloroform; all other signals accounted for and in accord with the structure. [c] All compounds showed the correct M^+ in the mass spectra. [d] Crystallized from methanol. [e] Without recrystallization.

Table I—Analytical Data for Carboxymethyl Carbodithioates (III)

Compound	Yield, %	Melting Point	Color[a]	PMR[b], δ SCH_2	λ_{max}, nm (log ε)	Formula
III*a*	66[c]	55–56°[d]	Y	4.08		$C_{10}H_{18}O_2S_2$
III*b*	62[c]	58–59.5°[d]	Y	4.06		$C_{12}H_{22}O_2S_2$
III*c*	75[c]	64.5–66°[d]	Y	4.05	306 (3.90)[e]	$C_{14}H_{26}O_2S_2$
III*d*	65[c]	72–73°[d]	Y	4.07	450 (1.26)[f]	$C_{16}H_{30}O_2S_2$
III*e*	65[c]	77.5–78.5°[d]	Y	4.08		$C_{18}H_{34}O_2S_2$
III*f*	69[c]	80.5–81.5°[d]	Y	4.07		$C_{20}H_{38}O_2S_2$
III*g*	89	113–114°[g]	P-R	4.30	293 (4.27)[e] 495 (2.21)[h]	$C_9H_7NO_4S_2$
III*h*	71	158–158.5°[i]	R	4.36	343 (4.51)[e] 455 (3.06)[e]	$C_{15}H_{12}N_2O_2S_2$
III*i*	74	126–127°[j]	O	4.24		$C_9H_7FO_2S_2$

[a] Y = yellow, P = purple, R = red, and O = orange. [b] Measured in deuterochloroform, except III*h* which was measured in acetone-d_6; all other signals accounted for and in accord with the structure. [c] Based on 1-thioacylpiperidine. [d] Crystallized from methanol–water. [e] In methanol. [f] In 50% aqueous ethanol. [g] Crystallized from benzene. [h] In aqueous sodium hydroxide, pH 9.6. [i] Crystallized from ethanol. [j] Crystallized from benzene–petroleum ether (bp 40–60°).

Table IV—Elemental Analysis of New Compounds

Compound	Found, %				Required, %			
	C	H	N	S	C	H	N	S
III*a*	51.1	7.7	—	27.5	51.25	7.74	—	27.36
III*b*	55.2	8.4	—	24.8	54.92	8.45	—	24.44
III*c*	57.8	8.95	—	22.2	57.88	9.02	—	22.07
III*d*	59.9	9.4	—	20.4	60.33	9.49	—	20.13
III*e*	62.7	9.8	—	18.2	62.38	9.89	—	18.50
III*f*	63.85	10.1	—	16.7	64.12	10.22	—	17.12
III*g*	42.4	2.8	5.35	25.0	42.01	2.74	5.45	24.92
III*h*	56.9	3.9	9.0	19.8	56.94	3.82	8.86	20.27
III*i*	47.1	3.0	—	28.3	46.93	3.06	—	27.85
I*a*	68.4	11.0	6.1	14.25	68.66	11.08	6.16	14.10
I*b*	70.0	11.3	5.4	12.7	70.52	11.44	5.48	12.55
I*c*	72.1	11.7	4.95	11.2	72.02	11.73	4.94	11.31
I*d*	73.3	11.85	4.6	10.4	73.24	11.97	4.50	10.29
I*e*	74.2	12.2	4.2	9.3	74.27	12.17	4.13	9.44
I*f*	75.4	12.3	4.0	8.6	73.13	12.34	3.81	8.72
I*h*	69.95	6.2	13.5	10.3	69.87	6.19	13.58	10.36
I*i*	64.8	6.3	—	14.6	64.54	6.32	—	14.35
I*j*	65.1	6.8	6.3	14.5	65.12	6.83	6.33	14.49
II*g*	43.3	4.5	7.2	8.2	43.20	4.40	7.20	8.24
II*h*	53.7	5.0	9.3	7.1	53.57	4.95	9.37	7.15
II*i*	46.3	4.6	3.8	8.9	46.42	4.73	3.87	8.85
II*j*	46.4	5.0	3.8	8.9	46.67	5.03	3.89	8.90
IV*g*	44.5	3.1	5.8	13.5	44.81	2.93	5.81	13.29
IV*h*	59.8	4.1	9.4	10.6	59.98	4.03	9.33	10.67
IV*i*	50.6	3.1	—	14.7	50.47	3.30	—	14.96
IV*j*	50.65	3.9	—	15.2	50.95	3.80	—	15.11
IV*k*	52.7	4.4	—	14.25	53.09	4.46	—	14.17
—[a]	69.7	7.0	6.7	—	69.55	6.81	6.76	—

[a] 1-(4-Fluorobenzoyl)piperidine.

those with the alkyl chain shorter than tridecyl are soluble in dilute aqueous alkaline solutions. By virtue of the chromophoric group C=S, carboxymethyl carbodithioates are colored compounds; aliphatic derivatives are yellow, and aromatic ones are reddish.

Hydrolysis of II gives *S*-carboxymethyl carbothioate (IV) (Table III), which can be distinguished from III by an upfield shift of the methylene protons in the carboxymethyl group because the diamagnetic anisotropy of the C=S group is larger than that of the C=O group (2).

The stretching vibration of the C=S group in III is at 1223–1200 cm^{-1}, in agreement with the literature (5).

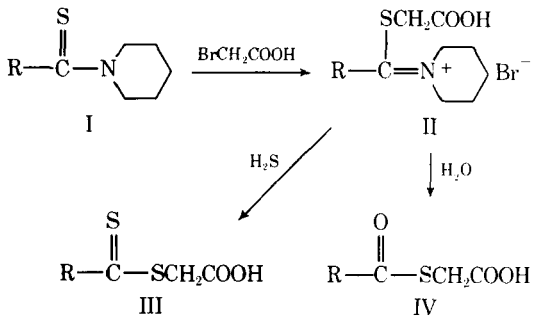
EXPERIMENTAL[1]

The following were prepared by the reaction of the acid chloride with piperidine in benzene: 1-lauroylpiperidine, bp 185°/2 mm [lit. (6) bp 185–187°/2–3 mm]; 1-myristoylpiperidine, bp 205–208°/2 mm [lit. (7) bp 206–209°/2 mm]; 1-palmitoylpiperidine, mp 35–37° (methanol) [lit. (8) mp 35–36°]; 1-stearylpiperidine, mp 43–44° [lit. (9) mp 44–44.5°]; and 1-(4-fluorobenzoyl)piperidine, mp 62–64° (petroleum ether, bp 40–60°). 1-(4-Nitrobenzoyl)piperidine (10) and 1-(4-phenylazobenzoyl)piperidine (11) were prepared by known methods.

1-Thiooctanoylpiperidine (Ia)—Caprylic aldehyde (19.2 g, 0.15 mole), piperidine (19.6 g, 0.23 mole), and sulfur (7.4 g, 0.23 mole) were mixed; the reaction mixture was refluxed for 3 hr, cooled slightly, and poured into water. The aqueous mixture was acidified with hydrochloric acid in the cold, and the orange oil was extracted with ether and dried (sodium sulfate). Evaporation of the solvent gave the crude product (28.3 g, 83%). Compound I*b* was obtained similarly.

1-Thiolauroylpiperidine (Ic)—Phosphorus pentasulfide (44.5 g, 0.2 mole) was added to a stirred solution of 1-lauroylpiperidine (107 g, 0.4 mole) in dry pyridine (200 ml), and the reaction mixture was refluxed for 3 hr with stirring. The hot solution was poured into a threefold volume of hot water with stirring. After 0.5 hr at room temperature, the mixture was cooled in ice with stirring. The precipitated oil soon solidified, and the brown solid was crystallized (methanol) and decolorized (charcoal) to give the product (87.3 g, 77%). Compounds I*d*–I*f*, I*g* [mp 179–180°; lit. (4) mp 176–178°], and I*h*–I*j* were similarly prepared. Compounds I*c*–I*j* were shown to be homogeneous (single spot on TLC, silica gel).

***S*-Carboxymethylthiolauroylpiperidinium Bromide (IIc)**—A solution of Ic (22.7 g, 70 mmoles) and bromoacetic acid (10.7 g, 77 mmoles) in dry ether (100 ml) was kept for 2 days at room temperature. The product, a pale-orange syrup, was separated by decanting the supernatant liquid, washed quickly (dry ether), and



a: R = $CH_3(CH_2)_6$ — *g*: R = 4-$NO_2C_6H_4$
b: R = $CH_3(CH_2)_8$ — *h*: R = 4-$(C_6H_5N{=}N)C_6H_4$
c: R = $CH_3(CH_2)_{10}$ — *i*: R = 4-FC_6H_4
d: R = $CH_3(CH_2)_{12}$ — *j*: R = 4-HOC_6H_4
e: R = $CH_3(CH_2)_{14}$ — *k*: R = 4-$CH_3OC_6H_4$
f: R = $CH_3(CH_2)_{16}$

Scheme I

[1] Melting points are uncorrected. IR spectra of solids and liquids were determined in potassium bromide disks and as pressed-out films on sodium chloride disks, respectively, with a Perkin-Elmer 257 instrument. UV and visible spectra were measured with Perkin-Elmer 137 and Unicam SP 500 spectrophotometers. PMR spectra were recorded with a JEOL-PS-100 (100 MHz) spectrometer (tetramethylsilane). Mass spectra were obtained with an AEI MS-9 spectrometer at an ionizing energy of 70 ev. Elementary analyses were performed by the Ilse Beetz Microanalytical Laboratory, Kronach, Germany (Table IV).

used immediately in the next reaction. Compounds II*a*, II*b*, and II*d*–II*f* were prepared similarly. The crude products were not analyzed.

***S*-Carboxymethyl-(4-nitrothiobenzoyl)piperidinium Bromide (II*g*)**—Bromoacetic acid (20.8 g, 0.15 mole) was added to a warm solution of I*g* (25.0 g, 0.1 mole) in dry ethylene dichloride (200 ml). After 2 days at 40°, the crystalline solid was filtered off, washed (dry ether), and dried *in vacuo* over phosphorus pentoxide to give the product (37 g, 98%). With benzene as the solvent at room temperature, previous workers (4) failed to prepare this compound.

***S*-Carboxymethyl-(4-phenylazothiobenzoyl)piperidinium Bromide (II*h*)**—A solution of I*h* (30.9 g, 0.1 mole) and bromoacetic acid (20.9 g, 0.15 mole) in dry benzene (600 ml) was kept for 2 days at room temperature. Workup as described for II*g* gave the product (31.4 g, 70%). Compound II*i* was obtained similarly; II*j* was prepared in dry chloroform.

Carboxymethyl Undecanecarbodithioate (III*c*)—A slow stream of dry hydrogen sulfide was passed for 3–4 hr through a stirred solution of II*c*, freshly prepared from I*c* (22.7 g, 70 mmoles), in dry dimethylformamide (85 ml). After 16 hr at 0–5°, the reaction mixture was poured into a threefold volume of ice water with stirring to give a yellow precipitate (14.8 g, 73% based on I*c*), mp 64.5–66° (methanol–water); ν_{max} 3000–2500 and 1710 (COOH) and 1224 (C=S) cm^{-1}; δ 10.4 (1H, s, COOH), 4.05 (2H, s, SCH_2), 3.00 (2H, t, J = 7.8 Hz, CH_2CS), 1.8 (2H, m, CH_2CH_2CS), 1.25 [16H, distorted s, $CH_3(CH_2)_8$], and 0.86 (3H, distorted t, CH_3). Compounds III*a*, III*b*, and III*d*–III*f* were obtained similarly. Attempts by previous workers (4), using ethanol as the solvent, failed to produce these compounds. Compounds III*g*–III*i* were prepared in absolute ethanol. Compounds III*a*–III*i* were shown to be homogeneous (single spot on TLC, silica gel).

***S*-Carboxymethyl 4-Nitrobenzenecarbothioate (IV*g*)**—Compound II*g* in 10 parts of water, after 16 hr at room temperature, gave the product as colorless needles. Compounds IV*h*–IV*k* were obtained similarly. Compounds IV*g*–IV*k* were shown to be homogeneous (single spot on TLC, silica gel).

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COMMUNICATIONS

Stereochemistry of Geometric Isomers of Clomiphene: A Correction of the Literature and a Reexamination of Structure–Activity Relationships

Keyphrases □ Clomiphene—stereochemistry of geometric isomers, structure–activity relationships □ Structure–activity relationships—clomiphene, geometric isomers

To the Editor:

The B-isomer of clomiphene[1] hydrochloride (I-HCl), 2-[*p*-(2-chloro-1,2-diphenylvinyl)phenoxy]triethylamine hydrochloride (IA-HCl, mp 156.5–158°; IB-HCl, mp 149–150.5°), was designated *cis* (Z) since it exhibits a UV λ_{max} attributed to a *trans*-*p*-alkoxystilbene chromophore at a higher wavelength than the A-isomer (1). A comparison of dipole moment, UV, IR, and PMR data of I geometric isomers, 2-[*p*-(2-bromo-1,2-diphenylvinyl)phenoxy]triethylamine (II) and *p*-(2-bromo-1,2-diphenylvinyl)anisole (III) (2), supported this conclusion. However, this conclusion rests on a tenuous stereochemical assignment for geometric isomers of III (3, 4).

In fact, based on a comparison of the dipole moments and spectra of isomers of I–III with those of isomers of 2-[*p*-(1,2-diphenyl-1-butenyl)phenoxy]-*N*,*N*-dimethylethylamine (IV), these assignments were inconsistent with the unequivocal crystallographic proof of stereochemistry for isomers of IV (5, 6). In addition, structure–activity relationships for these compounds were inconsistent since the *cis*-isomer of IV induces conventional estrogenic responses and is the more potent isomer in these respects (7–10), while IA, which had been assigned the *trans*-geometry, exhibits the conventional estrogenic responses and is the more potent isomer of I in these respects (11–21). Furthermore, while the *trans*-isomer of IV exhibits antiestrogenic actions (7–10), IB, previously designated *cis* (1, 2), is the antiestrogenic

[1] Clomid, Merrell-National Laboratories, Division of Richardson-Merrell Inc., Cincinnati, Ohio, is the citrate salt of an isomeric mixture.