Heteroatomic Chains and their Products of Cyclisation. IV. *t*-Butyl-2-phthalimido-2-(3,6-dihydro-1,3-2*H*-thiazine-2-yliden)-acetates Substituted in Position 5 by a Functional Group

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Substituted *N'*-thioacetylformamidines, readily enthiolized, exist in fact in the form of zwitterions **8** with the transfer of the mobile hydrogen on the nitrogen *N'*. These zwitterions under (4 + 2) cyclocondensation with dienophiles. The dihydrothiazines formed (**10**) are possible interesting intermediates in the synthesis of cephems and cephalosporin analogs.

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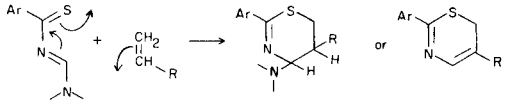
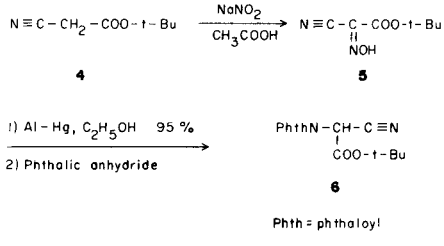
We have shown (2) that (4 + 2) cycloadditions between *N*-disubstituted thioacylformamidines **1** and dienophiles lead to dihydrothiazines **2** or thiazines **3** with elimination of the amino group. In this study, an aromatic substituent



1 **2** **3**

was attached to the thiocarbonyl group. This method provides thiazines **3** which can be obtained from relatively short reaction sequences and with good yields. With appropriate substitution, the thiazines can provide interesting intermediates for the synthesis of cephems and cephalosporin analogs (3,4).

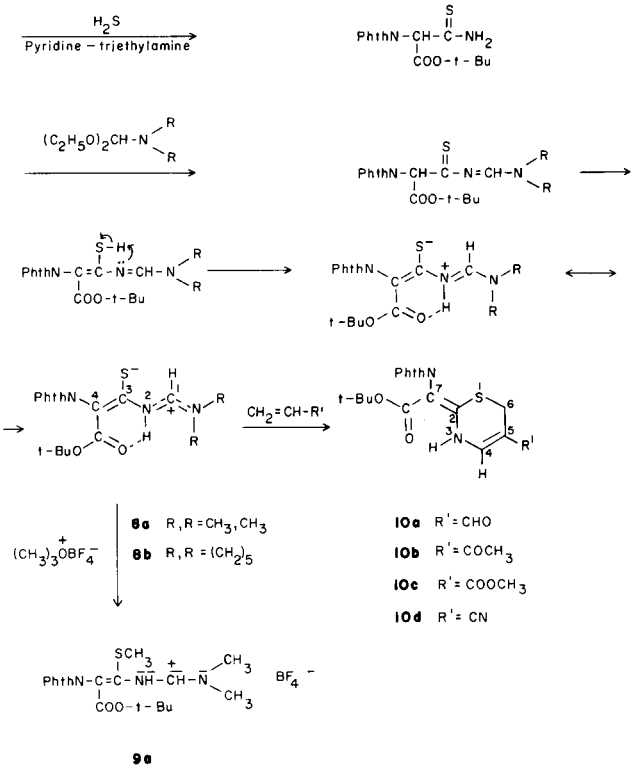
An approach to cephalosporins parallels the Sheehan strategy for the total synthesis of penicillins (5). This employs the stepwise construction of dihydrothiazines appropriately substituted at the 2-position to permit subsequent β-lactam ring formation. However, it was uncertain whether such thiazines could be made by our method which would require addition of a dienophile to the possibly enthiolized thioacylformamidine. This was verified by the following six-step sequence starting with *t*-butyl cyanoacetate.



4 **5**

6

Phth = phthaloyl



8a R,R = CH_3,CH_3
8b R,R = $(CH_2)_5$

10a R' = CHO
10b R' = $COCH_3$
10c R' = $COOCH_3$
10d R' = CN

9a

The pmr and cmr spectra of the compounds **8** are not in accordance with either the thioketone or the enthiol structures, but correspond to the zwitterionic structure indicated. This is supported by the coupling of the signal corresponding to the proton attached to carbon 1 with that of a proton which can only be attached to the 2-nitrogen (the nitrogen at the end of the chain retains its two non-equivalent methyl groups and is therefore not quaternized). In the -NH-CH- chain, the proton-proton coupling is

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Table I

Nmr Data

Compound No.	Solvent	Type	Chemical Shifts in Ppm, $J1_H1_H$ and $J13_C1_H$ Coupling Constants in Parentheses
8a	deuteriochloroform	pmr	9.44 (d, 1H, J = 12.0, H_1), 14.61 (d, 1H, J = 12.0, H_2), 1.37 (s, 9H, $(CH_3)_3$), 3.30 (s, 3H, N-CH_3), 3.43 (s, 3H, N-CH_3)
		cmr	153.5 (J = 195.5, C_1), 173.0 (C_3), 103.4 (C_4), 44.5 (J = 144.0, N-CH_3), 38.3 (J = 144.5, N-CH_3), 28.4 (J = 127.0, $(CH_3)_3$), 81.5 (C-O-), 168.3 (O-C=O), 168.3 (N-C=O), 132.8 (C_1'), 133.9 (J = 162.5, C_2'), 123.6 (J = 165.5, C_3') (a)
8b	deuteriochloroform	pmr	9.39 (d, 1H, J = 12.5, H_1), 14.53 (d, 1H, J = 12.5, H_2), 1.36 (s, 9H, $(CH_3)_3$), 1.82 (m, 6H, Hb, Hb' and Hc), 3.66 (m, 4H, Ha and Ha') (b)
		cmr	152.3 (J = 195.5, C_1), 173.4 (C_3), 104.1 (C_4), 48.0 and 54.6 (J = 141.5 and J = 141.5, C_a and C_a'), 25.0 and 26.2 (J = 130.0 and 128.5, C_b and C_b'), 23.1 (J = 129.0, C_c), 28.2 (J = 126.0, $(CH_3)_3$), 81.0 (C-O-), 167.8 (O-C=O), 168.1 (N-C=O), 132.6 (C_1'), 133.6 (J = 162.0, C_2'), 123.2 (J = 165.0, C_3')
10a	deuteriochloroform	pmr	11.62 (d, 1H, J = 6.0, H_3), 7.33 (dt, 1H, J = 6.0, J = 0.4, H_4), 3.60 (d, 2H, J = 0.4, H_6), 9.35 (s, 1H, CHO), 1.36 (s, 9H, $(CH_3)_3$)
		cmr	154.1 (C_2), 97.5 (C_7), 143.7 (J = 177.0, C_4), 112.7 (C_5), 19.4 (J = 147.0, C_6), 82.5 (C-O-), 28.0 (J = 127.0, $(CH_3)_3$), 167.1 (O-C=O), 187.2 (J = 173.0, CHO), 164.7 (N-C=O), 131.9 (C_1'), 134.3 (J = 164.5, C_2'), 123.6 (J = 167.0, C_3')
10b	deuteriochloroform	pmr	11.39 (d, 1H, J = 6.0, H_3), 7.51 (dt, 1H, J = 6.0, J = 0.5, H_4), 3.59 (d, 2H, J = 0.5, H_6), 2.31 (s, 3H, $COCH_3$), 1.33 (s, 9H, $(CH_3)_3$)
		cmr	154.8 (C_2), 96.2 (C_7), 137.1 (J = 176.0, C_4), 111.9 (C_5), 20.4 (J = 146.0, C_6), 82.1 (C-O-), 28.0 (J = 127.0, $(CH_3)_3$), 167.2 (O-C=O), 193.3 (CO of $COCH_3$), 164.9 (N-C=O), 131.9 (C_1'); 134.2 (J = 163.0, C_2'), 123.6 (J = 168.0, C_3')
10c	deuteriochloroform	pmr	11.26 (d, 1H, J = 6.0, H_3), 7.45 (dt, 1H, J = 6.0, J = 0.5, H_4), 3.57 (d, 2H, J = 1.0, H_6), 3.74 (s, 3H, $COOCH_3$), 1.35 (s, 9H, $(CH_3)_3$)
		cmr	154.6 (C_2), 96.2 (C_7), 135.8 (J = 181.0, C_4), 101.2 (C_5), 21.6 (J = 146.0, C_6), 82.0 (C-O- of $(CH_3)_3$-C-O), 28.0 (J = 127.0, $(CH_3)_3$), 167.4 (O-C=O of $(CH_3)_3$-O-C=O), 165.0 (CO of $COOCH_3$), 51.8 (J = 147.0, CH_3 of $COOCH_3$), 165.7 (N-C=O), 132.0 (C_1'), 134.2 (J = 163.0, C_2'), 123.6 (J = 167.0, C_3')
10d	dimethylsulfoxide-d_6	pmr	11.43 (d, 1H, J = 6.0, H_3), 7.08 (dt, 1H, J = 6.0, J = 0.95, H_4), 3.47 (d, 2H, J = 0.95, H_6), 1.36 (s, 9H, $(CH_3)_3$)
		cmr	152.4 (C_2), 97.3 (C_7), 138.7 (J = 182.0, C_4), 82.6 (CN), 23.2 (J = 147.5, C_6), 81.8 (C-O-), 28.0 (J = 127.0, $(CH_3)_3$), 167.2 (O-C=O), 118.0 (CN), 164.7 (N-C=O), 131.9 (C_1'), 134.4 (J = 163, C_2'), 123.7 (J = 168.0, C_3')

(a) The carbon atoms C_1', C_2', C_3' of the benzene ring are α,β and γ, respectively, to the C=O group. (b) Positions a and a', b and b' and c of the piperidine ring are α,β and γ, respectively, to the nitrogen atom.

12-12.5 Hz. The H of the NH resonates at 14.5-14.6, and its chemical shift can be explained by the C=O---H-N hydrogen bonding; the H of the CH also has a relatively high chemical shift (δ 9.4) due to the positive nature of the formamidinium chain (for a complete interpretation of the spectra, see Table I).

The formula attributed to compound **8a** and its zwitterionic character are clearly evident from the conversion **8a**→**9a**.

The pmr and cmr spectra of **10** are consistent with the structures indicated (6). In the pmr spectra, there is a CH of a highly shifted aromatic type (7.0-7.5), and NH (11.2-11.6) and a coupling constant of 6 Hz between the two protons. In the cmr spectra, four ethylenic carbons (including one CH) are observed, which are easily distinguishable from the three aromatic carbons.

EXPERIMENTAL

The nmr spectra were measured using a Varian XL 100-12 spectrometer, operating in continuous wave at 100 MHz for the proton and Fourier transform at 25.18 MHz for the carbon. The proton chemical shifts are accurate to within 0.02 ppm, and those of the carbon to within 0.1 ppm. The concentrations of the solutions in deuteriochloroform and hexadeuteriodimethylsulfoxide are of the order of 0.5 to 1 mole l^{-1}. The ir spectra were measured on a Unicam SP 1100 instrument (potassium bromide pellets). The mass spectra were measured on a Varian Mat 112 spectrometer (electron impact at 70 ev). Only the peaks for which the relative intensities are greater than or equal to 10% are recorded. The uv-visible absorption spectra were measured on a Beckmann DB-G spectrometer using methanol (where no indication was given) or methanol and 10% water. Concentrations were of the order of 2 to 4.10^{-5} mole l^{-1}. Microanalysis were carried out by the C.N.R.S. Microanalysis Service of Caen (France).

t-Butyl 2-Oximinocyanoacetate (**5**).

A mixture of 130 g. of sodium nitrite and 88 g. of *t*-butyl cyanoacetate

4 (7) in 600 ml. of water was stirred vigorously and 156 ml. of acetic acid was added dropwise over about 4 hours keeping the temperature between 10-15°. Stirring was continued for another 12 hours during which the product crystallised. The product was filtered, washed (ice water) and dried (vacuum, 40°) to constant weight (83 g.). The mother-liquor and the washings were combined and extracted with ether. The ethereal layer was washed with sodium bicarbonate solution then with water and dried. After evaporation and drying, another 7 g. of the compound **5** was obtained (85%) m.p. 74-75°; ir: 3180 cm^{-1} (OH), 1735, 1715 (C=O), 1635 (C=N).

t-Butyl 2-Phthalimidocyanoacetate (**6**).

Aluminium amalgam was made from 4 g. of (Albal) aluminium foil cut in strips. The amalgam was washed twice with a minimum of water and twice with a minimum of ethanol (95%). The amalgam was covered with 150 ml. of ethanol (95%) and 12 g. of the compound **5**, dissolved in a minimum of ethanol, was added using a magnetic stirrer. When all the aluminium had disappeared (about 30 minutes), the mixture was centrifuged and the precipitate was extracted twice with benzene. The alcohol and the benzene solutions were combined and evaporated using a rotatory evaporator to give 10 g. of *t*-butyl 2-aminocyanoacetate as a yellow oil.

The proceding yellow oil was dissolved in 100 ml. of toluene and 0.9 ml. of triethylamine was added followed by 15 g. of phthalic anhydride suspended in toluene. The flask containing the mixture was then placed in an oil-bath preheated to 180° and the contents stirred magnetically. The reaction media thickened and then became fluid again. Water was removed by azeotroping some of the toluene. The solution was filtered while hot to eliminate an insoluble white by-product. The filtrate was evaporated and the yellow crystalline residue was treated with 200 ml. of boiling water to dissolve excess phthalic anhydride. The crude product was dried and crystallised from aqueous ethanol. It was then washed with petroleum ether giving 12 g. (overall yield 50%) of white crystals, m.p. 145°; pmr: 1.55 (s, 9H, $(CH_3)_3$), 5.76 (s, 1H, CH), $\frac{\delta A' + \delta B'}{2}$ = 7.90 (AA'BB' system, 4H, phenylene); ir: 1790 cm^{-1} (sh), 1760, 1730, 1615 (C=O).

Anal. Calcd. for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.79. Found: C, 63.06; H, 4.88; N, 10.04.

t-Butyl 3-Amino-2-phthalimido-3-thioxopropionate (**7**).

Hydrogen sulphide was bubbled through a solution of 5.72 g. of **6** in 40 ml. of pyridine and 20 ml. of triethylamine at room temperature for 4-5 hours. The reaction mixture was then poured into 500 ml. of saturated sodium chloride solution (about 175 g.). This was extracted with benzene. The benzene solution was dried over sodium sulphate and concentrated. Xylene was added and the mixture distilled to remove pyridine if necessary. The residue was crystallised from ethanol giving pink crystals, m.p. 166-168° (93%). A final purification was carried out by chromatography on silica gel using aliquot of the order of 0.5 g., ir: 3380 cm^{-1}, 3160 (NH), 1780, 1722, 1615 (C=O).

Anal. Calcd. for $C_{15}H_{16}N_2O_4S$: C, 56.23; H, 5.03; N, 8.74; S, 10.01. Found: C, 56.20; H, 4.99; N, 8.67; S, 9.93.

t-Butyl 3-[(Dimethylamino)methylene]amino-2-phthalimido-3-thioxopropionate (**8a**) and *t*-Butyl 2-Phthalimido-3-[(piperidino)methylene]amino-3-thioxopropionate (**8b**).

Dimethylformamide diethylacetal was prepared according to Meerwein (8). Piperidinoformaldehyde diethylacetal was obtained by the transamination of the former by piperidine (9). Weidinger's method (10), slightly modified, was followed for the condensation. A suspension of equimolar quantities of the thioamide **7** and the diethylacetal in benzene was stirred for 2 hours. The precipitate which formed was filtered off and washed with ether. Purification was achieved by chromatography on silica gel using 0.5 g. aliquots. After elution with benzene, the compounds **8** were crystallised from acetonitrile (90% for both compounds **8a** and **8b**).

Compound **8a** was obtained as yellow crystals, m.p. 211-213°; ir: 1780 cm^{-1}, 1760, 1718, 1680, 1625 (C=O); uv (methanol/water): λ = 345 nm (ϵ 25,000), 264 (30,000), 240 (26,000, sh), 214 (36,000).

Anal. Calcd. for $C_{16}H_{21}N_3O_4S$: C, 57.58; H, 5.64; N, 11.20; S, 8.54. Found: C, 57.66; H, 6.11; N, 10.79; S, 8.32.

Compound **8b** was obtained as yellow crystals, m.p. 203-206°; ir: 1780 cm^{-1}, 1765, 1720, 1680, 1615 (C=O).

Anal. Calcd. for $C_{21}H_{25}N_3O_4S$: C, 60.70; H, 6.07; S, 7.72. Found: C, 60.11; H, 5.92; S, 7.65.

N-[(1-Methylthio-2-phthalimido-2-*t*-butoxycarbonylvinyl)aminomethylene]-dimethylammonium Tetrafluoroborate (**9a**).

Compound **8a** (1 g.) and 0.4 g. of trimethyloxonium tetrafluoroborate in 20 ml. of dichloromethane were refluxed, using a magnetic stirrer, for 2 hours. The solvent was evaporated and ether added to the residue. The fraction insoluble in the ether was crystallised from a dichloromethane-ether mixture giving white crystals (100%), m.p. 135-138°; pmr: δ 1.41 (s, 9H, $(CH_3)_3$), 2.44 (s, 1H, SCH_3), 3.51 (s, 3H, N-CH_3), 3.71 (s, 3H, N-CH_3), 8.84 (s, 1H, H_1); cmr: δ 154.0 (J = 203.5, C_1), 152.1 (C_3), 112.3 (C_4), 45.4 (J = 144.0, N-CH_3), 38.5 (J = 144.0, N-CH_3), 17.7 (J = 146.5, SCH_3), 164.7 (O-C=O), 85.9 (C-O- of $(CH_3)_3C$-O), 27.7 (J = 128.0, $(CH_3)_3$), 166.5 (N-C=O), 131.5 ($C_{1'}$), 135.1 (J = 163.0, $C_{2'}$), 124.1 (J = 166.0, $C_{3'}$).

Anal. Calcd. for $C_{19}H_{24}BF_4N_3O_4S$: C, 47.81; H, 5.07; S, 6.72. Found: C, 47.65; H, 5.16; S, 6.60.

t-Butyl-2-phthalimido-2-(3,6-dihydro-1,3-2*H*-thiazine-2-yliden)acetates (**10**).

The acrylic dienophile was used in great excess compared to **8a** or **8b** except for acrolein which was used in a smaller excess.

The compounds **10b, 10c** and **10d** were obtained as follows: 20 ml. of methylvinylketone (or methylacrylate or acrylonitrile) and 0.1 g. of hydroquinone were added to 25 ml. of benzene containing 4 g. of **8a**. The mixture was heated under reflux in an oil bath for 24 hours. The liquid phase was then removed using a rotatory evaporator. The residue was redissolved in benzene and chromatographed on neutral alumina deactivated by suspension in benzene containing 5% water. Elution was carried out using ethyl acetate. Evaporation of the solvents gave a solid which was crystallised from ethanol.

Compound **10b** was obtained as white crystals (70%), m.p. 185-187°; ir: 3190 cm^{-1} (NH), 1785, 1725, 1665, 1640 (C=O), 1565 (C=C), ms: M^+ = 400 (22), 345 (22.5), 344 (100), 311 (19), 301 (12), 300 (27.5), 299 (14), 298 (10), 284 (15), 283 (44), 267 (26), 258 (14), 257 (22), 256 (19), 255 (19), 225 (12.5), 203 (20), 190 (17.5), 160 (60), 158 (11), 153 (44), 133 (10), 132 (20.5), 130 (11), 111 (14), 105 (13), 104 (64), 77 (14), 76 (34), 57 (29), 50 (13), 43 (53), 41 (27), 39 (11), 29 (14); uv: λ = 342 nm (ϵ 30,000), 235 (21,000, sh), 214 (32,000).

Anal. Calcd. for $C_{20}H_{20}N_2O_5S$: C, 59.98; H, 5.03; N, 7.00; S, 8.01. Found: C, 60.06; H, 5.15; N, 7.02; S, 8.02.

Compound **10c** was obtained as white crystals (91%) m.p. 164-167°; ir: 1785 cm^{-1}, 1722, 1700, 1670 (C=O), 1570 (C=C); ms: M^+ = 416 (2), 360 (19.5), 283 (10.5), 203 (23), 190 (11), 169 (92), 160 (68), 156 (13), 133 (12), 132 (23.5), 130 (11), 114 (19.5), 105 (17.5), 104 (100), 82 (11.5), 77 (19), 76 (37.5), 57 (25), 56 (21), 50 (17), 45 (52.5), 41 (50), 40 (29.5), 39 (22.5); uv: λ = 337 nm (ϵ = 33,000), 230 (22,000 sh), 213.5 (39,000).

Anal. Calcd. for $C_{20}H_{20}N_2O_6S$: C, 57.68; H, 4.84; S, 7.70. Found: C, 57.74; H, 5.01; S, 7.78.

Compound **10d** was obtained as white crystals (70%), m.p. 210-214°; ir: 3300 cm^{-1}, 3180 (NH), 2205 (C=N), 1790, 1725, 1665, 1645 (C=O), 1575 (C=C); ms: M^+ = 383 (3.8), 328 (12), 327 (71.5), 310 (18), 203 (54), 190 (24), 160 (48), 136 (59), 133 (11.5), 132 (65), 130 (12.5), 105 (14), 104 (100), 78 (10), 77 (21), 76 (45), 57 (85), 56 (17), 51 (10), 50 (21), 44 (28), 41 (59), 39 (22).

Anal. Calcd. for $C_{19}H_{17}N_3O_4S$: C, 59.51; H, 4.47; S, 8.36. Found: C, 59.71; H, 4.67; S, 8.19.

Compound **10a** was obtained as follows: a mixture of 2 g. of **8a**, 1.5 ml. of acrolein and 0.1 g. of hydroquinone in 50 ml. of benzene was heated slowly to reflux with magnetic stirring. Refluxing was continued for 17 hours. The rest of the method was as described above. Compound **10a** was obtained as pale yellow crystals (66%), m.p. 180-182°; ir: 3180 cm^{-1}, 3130 (NH), 1788, 1765, 1722, 1670, 1660, 1645 (C=O), 1585 (C=C); ms: M^+ = 386 (2.5), 330 (27), 286 (13.5), 283 (15.5), 256 (10), 255 (10.5), 225 (11), 203

(31), 163 (17), 160 (67), 139 (87.5), 133 (17), 132 (54), 130 (16), 111 (10.5), 105 (20), 104 (100), 84 (17.5), 77 (25), 76 (75), 57 (50), 56 (19), 55 (11), 51 (11), 50 (23), 44 (34.5), 41 (62.5), 40 (12.5), 39 (25); uv: λ = 346 nm (ϵ = 28,000), 238 (21,000, sh), 218 (30,000).

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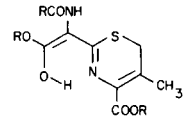

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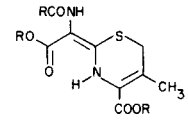

B

cephalosporin lactam ring by an alkoxide (on the condition that a final esterification is possible). The analogy of the chemical shifts of the hydrogens attached to the endocyclic nitrogen atoms (11.1 and 11.2 for Lowe, *et al.,* about 11.4 for the compounds **10** described in this publication) suggests that, in both cases, it is a question of dihydrothiazines and not thiazines (**B** instead of **A**).

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