Unusual Azetidine or Oxazine Formation upon Reaction of *O*-Ethyl Dithiocarbonate with 1,2,3-Triphenyl-3-Phthalimidopropyl Iodides; *Erythro* Selectivity in the Reaction of Iodotrimethylsilane with Phthalimidopropanols†

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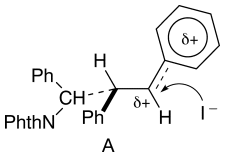
M. E. Ivanova, V. B. Kurteva, M. J. Lyapova* and I. G. Pojarlieff

Institute of Organic Chemistry, Bulgarian Academy of Sciences, ul. Acad. G. Bonchev block 9, Sofia 1113, Bulgaria

Reaction of isomeric 1,2,3-triphenyl-3-phthalimidopropanols with hexamethyldisilane and iodine gave highly selectively iodides **3** with 1,2-*erythro* configuration which treated with *O*-ethyl dithiocarbonate yielded from *ET*-**3** the xanthate ester **4**, the *trans*,*trans*-dihydrooxazine **5** and the olefin **6** as major products while from *EE*-**3** the *cis*,*trans*-azetidine **7** was obtained in 75% yield.

Our long standing interest in diastereomers with three adjacent chiral centers has been focused on aminopropanols.[1] In an extention to aminothiols we attempted to prepare 1,2,3-triphenyl-3-phthalimidopropyl dithiocarbonates from the respective alcohols **1** *via* the chlorides **2**. The latter proved too unreactive to *O*-ethyl dithiocarbonate and for this reason the iodides, **3**, were prepared from **1** with iodotrimethylsilane. High yields were obtained and, contrary to the usually observed inversion of configuration,[2] this reaction showed high *erythro* selectivity with the sterically hindered alcohols studied by us: *EE*-**1** gave a single 3-phthalimido iodide of retained configuration while both *TT*- and *ET*-**1** gave *ET*-**3**. This stereochemical result can be rationalized by the involvement of a carbenium ion. As is the case with methine protons next to sp^2 carbons,[3] the preferred conformation for the cation should be the one with eclipsed hydrogen and a partial double bond. With such a model (**A**) the preferred attack should be from the side of the smaller substituent Ph, compared to C-3.

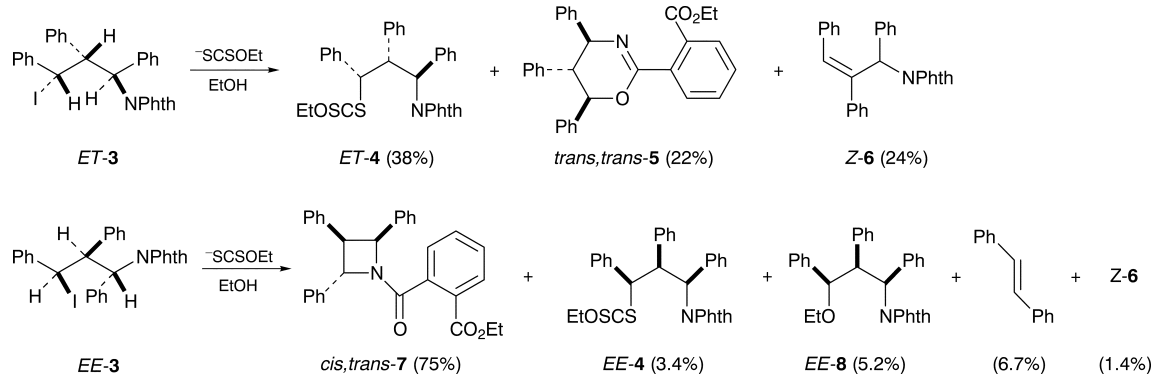


A

Reaction of the iodides **3** with ethyl dithiocarbonate in dry ethanol gave the desired phthalimidopropyl dithiocarbonate **4** as a major product only in the case of *ET*-**3** accompanied by considerable amounts of the unexpected oxazine **5** and the elimination product **6**. With the *EE* isomer of **3**, however, a high yield of the *cis*,*trans*-azetidine **7** was obtained.

The structure of the cyclic products was deduced from their spectral properties indicating opening of the phthalimide ring and formation of an ester function. Acid hydrolysis of oxazine **5** to *TT*-3-amino-1,2,3-triphenylpropanol confirmed reliably its structure. The ^{13}C NMR signals for C-2 and C-4 of the azetidine **7** coinciding at δ 61.88 are incompatible with an oxazine structure where one carbon is bonded to O and the other one to N and thence a large difference in the chemical shifts is expected. For oxazine **5** the resonances of the two carbons are separated by 18 ppm.

Heating the iodides in ethanol in the absence of dithiocarbonate brought about degradation but none of the cyclic products, implying that dithiocarbonate is involved by adding to a carbonyl. The intermediate forms the oxazine ring by rear attack followed by ethanolysis. For azetidine formation the intermediate breaks down to produce an amide anion. The conformations of the iodides on Scheme 1 are the preferred ones[6] and correlate with cyclization reactivities: in the *ET* isomer O^- can be trapped by direct attack, in the *EE* isomer changing to an unfavourable



Scheme 1

conformation presumably allows time for break down to amide anion.

Cyclization of addition intermediates has been observed in the reaction of aldimine anions with *N*-(2-

*To receive any correspondence.

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Table 1 ^{1}H NMR chemical shifts (δ) and coupling constants (in Hz, in parentheses)

Compound	H-1(J_{12})	H-2[a]	H-3(J_{23})
EE-**1**[b]	4.82(2.8)	4.69	6.21 (13.2)
ET-**1**[c]	5.08(4.20)	4.77	6.11(12.2)
TT-**1**[d]	5.083(4.5)	4.956	6.076(11.9)
EE-**3**	5.084(3.1)	4.021	5.931(11.9)
ET-**3**	5.525(6.9)	4.665	5.810(11.6)
EE-**4**[e]	5.136(3.6)	5.250	5.490(12.6)
ET-**4**[f]	5.421(3.6)	5.319	5.666(12.3)
trans,trans-**5**[g]	5.030(10.4)[h]	3.136[i]	5.491(10.7)[j]
Z-**6**	6.415(1.9)[k,l]		6.484(1.9)[k,l]
cis,trans-**7**[m]	5.033(5.4)[n]	3.812[o]	5.590(9.9)[p]
EE-**8**[q]	4.280(2.9)	4.432	6.213(12.3)

[a]Couplings not shown. [b]OH 1.78(6.0). [c]OH 1.98(4.6). [d]OH 2.096(4.5). [e]CH_2 4.504, CH_3 1.232. [f]CH_2 4.470, CH_3 1.225. [g]CH_2 4.237, CH_3 1.282. [h]H-4(J_{45}). [i]H-5. [j]H-6(J_{56}). [k]J_{13}. [l]No NOE enhancement was observed. [m]CH_2, 4.202, CH_3 1.230. [n]H-2(J_{23}). [o]H-3. [p]H-4(J_{45}). [q]CH_2 3.203, CH_3 1.960.

bromoethyl)phthalimides.[4] The involvement of the amide anion in the formation of the azetidine is supported by the presence of stilbene observed in the fragmentation of a similar system.[1]

The relative configurations at C-2, C-3 are not affected in these reactions and so are known from the starting phthalimido propanols **1**.[5] Azetidine **7** shows vicinal proton couplings of 5.4 and 9.9 Hz thus revealing a *cis*,*trans* configuration because with equal substituents in positions 2 and 4 the other alternative, the *cis*,*cis* isomer, would show equal constants. Slow rotation on the NMR timescale can be excluded as it would have doubled the signals of *cis*,*trans*-**7**. The oxazine **5** shows the characteristic large couplings of the *trans*,*trans* isomer. The most likely intramolecular cyclization by inversion at C-1 assigns the relative configurations of the idodides as given in Scheme 1.

The configurations of the dithiocarbonates **4** were only tentatively assigned. In the case *EE*-**3** the configuration of the ether **8** was unequivocally assigned by synthesis from the alcohol *EE*-**1** and ethyl iodide and its configuration can be explained by the model given for the iodides. The same pathway will provide *EE*-dithiocarbonate from *EE*-**3** and the *ET* isomer for *ET*-**3**.

Experimental

The melting points were measured in capillaries, the IR spectra on a Specord IR 75 or Bruker IFS 113v instrument in chloroform unless stated otherwise, UV spectra on a Specord UV Vis spectrometer in ethanol, NMR spectra on a Bruker DRX 250 in deuteriochloroform (chemical shifts are quoted in ppm as δ values) and mass spectra on a JEOL JMS-D 300 spectrometer.

EE-1,2,3-*Triphenyl*-3-*phthalimidopropanol* **1**.—A solution of *EE*-3-amino-1,2,3-triphenylpropanol[7] (303 mg, 1 mmol) and phthalic anhydride (148 mg, 1 mmol) in dry pyridine (1 ml) was refluxed for 2 h. After cooling the mixture was poured onto ice and allowed to stand overnight. The separated material was triturated with 10% HCl (50 ml), the solid formed was collected and recrystallized from ethanol to give compound *EE*-**1** (516 mg, yield 95%), mp 217–218 °C; $\tilde{\nu}_{max}$ 1710, 1760, 3400 cm^{-1}; MS (Cl) $[M+1]^+$ *m*/*z* 434, 416, 374, 270, 254, 210 (Found: C, 80.12; H, 5.35; N, 3.18. $C_{29}H_{23}NO_3$, requires C, 80.35; H, 5.35; N, 3.23%).

Diastereomeric 1,2,3-*Triphenylpropyl*-3-*phthalimido Iodides* (**3**)*: General Procedure*.—Iodine (254 mg, 1 mmol) and hexamethyldisilane (0.2 ml, 1 mmol) were added to a stirred solution of the appropriate phthalimidopropanol (434 mg, 1 mmol) in dry chloroform (5 ml) under argon. After 4 h of stirring at room temperature the reaction mixture was rapidly extracted with 10% $Na_2S_2O_3$ (aq), the organic layer was washed with brine, dried (Na_2SO_4) and evaporated to dryness under reduced pressure.

EE-**3**. From *EE*-**1**, as a single diastereoisomer (NMR), yield 95%, mp 145–147 °C (decomp.); $\tilde{\nu}_{max}$ 1710, 1760 cm^{-1}; MS (Cl) $[M+1]^+$ *m*/*z* 544, 416, 269, 254, 236, 180, 150, 128.

ET-**3**. (a) From *ET*-**1**,[5] crude yield 420 mg, mp 177–179 °C (chloroform–hexane, 59%); $\tilde{\nu}_{max}$ 1710, 1760 cm^{-1}; MS (EI) $[M-I]^+$ 415, 269, 268, 254, 236, 180, 150, 128, 127.

(b) From *TT*-**1**, as a mixture of *ET*-**3**/*ET*-**1**/*TT*-**1** in a ratio of 4.4:1:1.2 (NMR) 480 mg.

Reaction of Phthalimido Iodide ET-**3** *with Potassium O-ethyl Dithiocarbonate*.—*ET*-**3** (4.9 g, 9 mmol) and $KS_2C(OEt)$ (4.3 g, 27 mmol) in dry ethanol (400 ml) was refluxed for 6 h. After removal of the solvent *in vacuo* the residue was extracted with CH_2Cl_2–water, the organic layer washed with brine, dried (Na_2SO_4) and evaporated. The crude reaction product which showed on TLC more than eight closely moving spots was separated by flash chromatography on Silica gel (ether–hexane 1:4 as eluent) giving four major products: trans,trans-5,6-*dihydro*-4H-2 (2-*ethoxycarbonylphenyl*)-4,5,6-*triphenyl*-1,3-*oxazine* **5** (800 mg, 22%), mp 128–130 °C (diisopropyl ether); $\tilde{\nu}_{max}$ 1673, 1715 cm^{-1}; ^{13}C NMR (DEPT) C-2 δ 157.21, C-4 64.29, C-5, 53.33, C-6 81.83, COO 167.63, CH_2 61.10, CH_3 14.17; MS (CI) $[M+1]^+$ *m*/*z* 462, 416, 284, 236, 180, 149 (Found: C, 80.82; H, 5.74; N, 3.18. $C_{31}H_{27}NO_3$, requires C, 80.67; H, 5.90; N, 3.03%); ET S-O-*ethyl*-1,2,3-*triphenylpropyl*-3-*phthalimido dithiocarbonate* **4** (1.4 g, 38%), mp 162–163 °C (ether–pentane); $\tilde{\nu}_{max}$ 1050, 1710, 1760 cm^{-1}; λ_{max} 385 nm ($SCSOC_2H_5$); MS(EI) $[M-SCSOC_2H_5]^+$ *m*/*z* 416, 268, 236, 180, 122($SCSOCH_2H_5$) (Found: C, 71.54; H, 5.20; N, 2.50; S, 11.81. $C_{32}H_{27}NO_3S$ requires C, 71.48; H, 5.06; N, 2.60; S, 11.92%); z-1,2,3-*triphenyl*-3-*phthalimidoprop*-1-*ene* **6** (864 mmg, 24%), mp 197–199 °C (chloroform–hexane); $\tilde{\nu}_{max}$ 1710, 1760 cm^{-1}; MS(CI) 416, 268, 236, 180 (Found: C, 83.89; H, 5.00; N, 3.59. $C_{29}H_{21}NO_2$ requires C, 83.83; H 5.09; N, 3.37).

Reaction of Phthalimido Iodide EE-**3** *with Potassium O-ethyl Dithiocarbonate*.—A solution of EE-**3** (2.71 g, 5 mmol) and $KS_2C(OEt)$ (2.7 g, 15 mmol) in absolute ethanol (150 ml) was treated in a manner to that described for *ET*-**3** to leave a residue, which was recrystallized from diisopropyl ether to give 1.04 g of cis,trans-N-(2-*ethoxycarbonylbenzoyl*)-2,3,4-*triphenylazetidine* **7**. A further 0.69 g could be isolated from the evaporated mother-liquor after separation on Silica gel (ether–hexane 1:4 as eluent), total yield 75%, mp 145–147 °C; $\tilde{\nu}_{max}$ 1660, 1715 cm^{-1}, ^{13}C NMR C-2 and C-4 δ 61.88 (common signal), C-3, 48.52, CO 156.93, COO 168.30, CH_2 61.23, CH_3 14.17; MS (CI) $[M+1]^+$ *m*/*z* 462, 282, 177 (Found: C, 80.54; H, 5.92; N, 3.24. $C_{31}H_{27}NO_3$, requires C, 80.67; H, 5.90; N, 3.03%). Four other products were isolated from the column: EE-*O-ethyl* S-1,2,3-*triphenyl*-3-*phthalimidopropyl dithiocarbonate* **4** (90 mg, 3.4%), mp 182–184 °C (diisopropyl ether); $\tilde{\nu}_{max}$ 1050, 1710, 1760 cm^{-1}; λ_{max} 385 nm ($SCSOC_2H_5$); MS(EI) [*M*-CS_2] *m*/*z* 460, [*M*-$SCSOC_2H_5$] 415, 324, 268, 236, 178, 151, 77(CS_2); EE-*ethyl* 1,2,3-*triphenyl*-3-*phthalimidopropyl ether* **8** (120 mg, 5.2%), mp 222–224 °C (diisopropyl ether); $\tilde{\nu}_{max}$ 1100, 1710, 1760 cm^{-1}; ESI-FTICR MS *m*/*z* 462.2049 (*M* + 1, theoretically 462.2064, $C_{31}H_{28}NO_3$) identical with the product obtained from *EE*-**1** (1 mmol), NaH (4 mmol) and ethyl iodide (4 mmol) in THF (5 ml) for 6 h at room temperature in 83% yield; **6** (30 mg, 1.4%), identical with the product obtained from *ET*-**3** in the same reaction; trans-stillbene (60 mg, 6.7%), identical with an authentic sample.

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