Synthesis of Some Phenyl Carboxymethyl Esters of Carbonic Acid and Its Sulfur Analogues

ERKKI HONKANEN

Research Department, Orion Oy, Pharmaceutical & Chemical Laboratories, Helsinki, Finland

Carbonic acid derivatives of the type III (R = H), in which X, Y, and Z are oxygen or sulfur atoms, have not been described in the literature. Recently, Jensen *et al.*[1] made some attempts to synthesize the compound IIId (R = H) from potassium *O*-phenyl dithiocarbonate and chloroacetic acid or from phenoxythiocarbonyl chloride (I, X = O, Y = S) and mercaptoacetic acid. Both of these routes of synthesis were, however, unsuccessful and yielded *O,O'*-diphenyl monothiocarbonate or bis(carboxymethyl) trithiocarbonate. No success was achieved in this laboratory when attempts were made to condense various compounds of the type I with hydroxy- or mercaptoacetic acid. When, however, the carboxyl group in these acids was protected by esterification (compounds II), the condensation with I proceeded normally and yielded the ester derivatives III in good yield.

$$\underset{\text{I}}{\text{Ph-X-}\overset{\overset{\text{Y}}{\|}}{\text{C}}\text{-Cl}} + \underset{\text{II}}{\text{HZ-CH}_2\text{COOR}} \rightarrow \underset{\text{III}}{\text{Ph-X-}\overset{\overset{\text{Y}}{\|}}{\text{C}}\text{-Z-CH}_2\text{COOR}}$$

X,Y,Z = O or S
R = *tert*-Bu or H

To liberate the acids (III, R = H) from these esters, the alkyl group R must be removed selectively in very mild conditions. Attempts to hydrolyze the methyl esters with the theoretical amounts of alkali were unsuccessful. When, however, the carboxyl group was protected by a *tert*-butyl group, it was possible to obtain the free acids using cold trifluoroacetic acid or *p*-toluenesulfonic acid in boiling benzene solution as a selective splitting agent. The compounds synthesized (Table 1) except compound IIIh, which was bright yellow, were almost colorless, crystalline solids. Because *p*-toluenesulfonic acid in boiling benzene solution caused the decomposition of the compounds IIId and IIIh to bis(carboxymethyl) trithiocarbonate as the main product, it was better to use cold trifluoroacetic acid to remove the *tert*-butyl group from these esters. In both cases, bis(carboxymethyl) trithiocarbonate was obtained as a by-product.

The needed *tert*-butyl mercaptoacetate (II, Z = S) has not been described before. It was synthesized by ammonolysis of *O*-ethyl-S-(*tert*-butyloxycarbonylmethyl) dithiocarbonate (IV) prepared by condensation of potassium *O*-ethyl dithiocarbonate with *tert*-butyl chloroacetate:

$$\text{C}_2\text{H}_5\text{OCS}_2\text{K} + \text{ClCH}_2\text{COO-}t\text{-Bu} \rightarrow \underset{\text{IV}}{\text{C}_2\text{H}_5\text{OCS}_2\text{CH}_2\text{COO-}t\text{-Bu}} \xrightarrow{\text{NH}_3} \underset{\text{II}}{\text{HSCH}_2\text{COO-}t\text{-Bu}}$$

tert-*Butyl hydroxyacetate* was prepared from *tert*-butyl bromoacetate according to Carpino.[2] It was isolated as a crystalline solid, m.p. 30–31°C, b.p.$_{10}$ 53°C (lit.[2] b.p.$_{52}$ 74–75°C).

O-*Ethyl* S-(tert-*butyloxycarbonylmethyl*) *dithiocarbonate* (IV). To a suspension of 176 g (1.1 mole) of potassium *O*-ethyl dithiocarbonate in 500 ml of dry acetone held at 10–15°C was added 151 g (1 mole) of *tert*-butyl chloroacetate with stirring. The mixture was stirred for 24 h at room temperature. Potassium chloride was filtered off and the solvent evaporated under vacuum. The oily residue was dissolved in ether and the solution washed thoroughly with an aqueous sodium hydrogen carbonate solution and then with water. After drying, the solvent was evaporated and the residue distilled under vacuum: b.p.$_8$ 135°C. (Traces of acidic impurities cause decomposition of the product on distillation. The crude product can be used without purification in the next step). Yield 208 g (88 %). (Found: C 46.03; H 6.98. Calc. for $C_9H_{16}O_3S_2$: C 45.74; H 6.82).

tert-*Butyl mercaptoacetate* (II, Z=S, R=*tert*-Bu). 90 g of crude IV was dissolved in 300 ml of ether and the solution saturated with dry ammonia at 0°C. After it had stood for 24 h at 0°C, the solution was filtered from *O*-ethyl

Table 1. Phenyl carboxymethyl esters of derivatives of carbonic acid, Ph-X-C(=Y)-Z-CH_2COOR.

Compound	X	Y	Z	R = *tert*-Bu	R = H				
				B.p. Yield,%	Formula	M.p.	Method	Yield %	Analyses
									C H S
IIIa	O	O	O	115°C/0.5 96	$C_9H_8O_5$	100–102°C	A	80	Calc.: 55.11 4.11 —
									Found: 55.34 4.09 —
IIIb	O	S	O	120°C/0.7 74	$C_9H_8O_4S$	115–117°C	A	50	Calc.: 50.94 3.80 15.11
									Found: 50.77 3.89 14.68
IIIc	O	O	S	130°C/0.6 94	$C_9H_8O_4S$	93–95°C	A	40	Calc.: 50.94 3.80 15.11
									Found: 51.24 3.88 14.55
IIId	O	S	S	Decomp. 95[a]	$C_9H_8O_3S_2$	65–68°C	B	58	Calc.: 47.35 3.54 28.09
									Found: 47.49 4.11 28.23
IIIe	S	O	O	120°/0.5 84	$C_9H_8O_4S$	82–85°C	A	84	Calc.: 50.94 3.80 15.11
									Found: 51.31 3.95 15.14
IIIf	S	S	O	150°C/2 Decomp. 61	$C_9H_8O_3S_2$	103–105°C	A	25	Calc.: 47.35 3.54 28.09
									Found: 48.02 3.58 27.91
IIIg	S	O	S	Decomp. 89[a]	$C_9H_8O_3S_2$	122–125°C	A	27	Calc.: 47.35 3.54 28.09
									Found: 47.40 3.94 28.11
IIIh	S	S	S	Decomp. 95[a]	$C_9H_8O_2S_3$	108–110°C	B	25	Calc.: 44.23 3.30 39.37
									Found: 44.77 3.63 38.85

[a] Yield of crude product.

thiocarbamate. The solvent was evaporated and the residue distilled under vacuum: b.p.$_6$ 44°C. The residue in the distillation flask was dissolved in ether and saturated with ammonia and the procedure continued as above. This procedure was repeated once again. In all 64 g (96 %) of *tert*-butyl mercaptoacetate, a colorless liquid, was obtained, which did not solidify on keeping several months in refrigerators at 5°C and −25°C. (Found: C 48.76; H 7.73; S 21.56. Calc. for $C_6H_{12}O_2S$: C 48.62; H 8.16; S 21.64).

General procedure for the preparation of compounds III (R = *tert*-butyl): 0.05 mole of *tert*-butyl hydroxyacetate or *tert*-butyl mercaptoacetate was dissolved in 50 ml of dry benzene containing 0.05 mole of triethylamine. To each of these solutions at 10°C was added with stirring 0.05 mole of the appropriate halogen compound (I) in 25 ml of dry benzene. After it had stood for 24 h at room temperature, each mixture was washed with water and dried over sodium sulfate. The solvent was evaporated and the residue distilled, if possible, under vacuum.

Removal of the tert*-butyl group with* p*-toluenesulfonic acid (method A)*: 10 g of each of the above *tert*-butyl esters was dissolved in 100 ml of dry benzene and 0.1 g of *p*-toluenesulfonic acid was added. The solutions were boiled under reflux for 1 h, after which they were washed with water. The solvent was evaporated and the residues crystallized from benzene-petroleum ether.

Removal of the tert*-butyl group with trifluoroacetic acid (method B)*: To 5 g of each of the *tert*-butyl esters (IIId or IIIh) was added 20 ml of 98 % trifluoroacetic acid with stirring at 0°C. The mixtures were allowed to stand for 30 min, after which the trifluoroacetic acid was evaporated under vacuum below 20°C. 50 ml of benzene was added and

the insoluble bis(carboxymethyl) trithiocarbonate (m.p. 171–173°C) was filtered off. The filtrates were treated with charcoal, concentrated and diluted with petroleum ether, whereupon the products crystallized.

1. Jensen, K. A., Anthoni, U. and Holm, A. *Acta Chem. Scand.* **23** (1969) 1916.
2. Carpino, L. *J. Org. Chem.* **29** (1964) 2820.

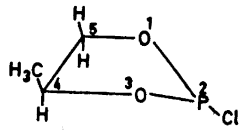
Received March 31, 1970.

Conformational Isomers of 1,2-Oxaphospholanes

KNUT BERGESEN

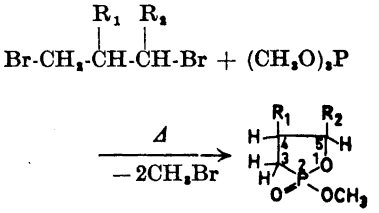
Chemical Institute, University of Bergen, Bergen, Norway

Conformational isomers of disubstituted five-membered rings, containing tervalent and quadruply linked phosphorus as heteroatom, are observed by several workers.[1–4] Goldwhite [1] has shown that the proton magnetic resonance spectrum of the cyclic compound, 2-chloro-4-methyl-1,3,2-dioxaphospholane (I), contains two



I

doublets centered at 0.95 and 1.20 ppm. The doublets were assigned to the methyl group placed in two different conformational environments, *cis* and *trans* to the 2-chlorosubstituent in compound (I). A similar interpretation accounts for the PMR spectra of other substituted 1,3,2-oxaphospholanes.[1,3] This paper reports the preparation of 2-methoxy-5-methyl-2-oxo-1,2-oxaphospholane (II) and 2-methoxy-4-methyl-2-oxo-1,2-oxaphospholane (III), prepared from trimethylphosphite and the dibromides 1,3-dibromobutane and 2-methyl-1,3-dibromopropane, respectively, on heating:



II: $R_1 = H, R_2 = CH_3$
III: $R_1 = CH_3, R_2 = H$

The structures of (II) and (III) were established by infrared and PMR spectra, as well by elementary analysis. Gaschromatographic analysis of (II) and (III) under several conditions has given one major peak only, but the PMR spectra indicate that these compounds are mixtures of conformational isomers in ratio approx. 2:1.

The PMR signal of the methyl group in position 5 in (II) is well separated from the rest of the spectrum and consists of two double doublets (Fig. 1). This is due

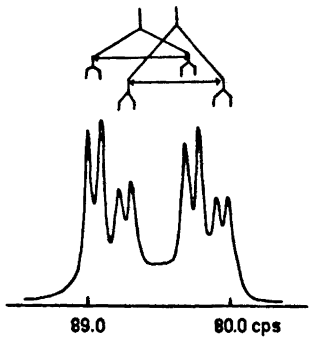


Fig. 1. Spectrum at 60 Mc of the methyl group in II in $CDCl_3$ with TMS as internal standard.

to the methyl groups in two different conformational environments coupled to the methine proton and to the phosphorus atom (Table 1). The PMR signal of the methyl groups in position 4 in (III) consists of two triplets (Fig. 2). It is assumed that the methyl group is coupled to phosphorus in only one of the two conformations of (III). A corresponding observation is also reported for 2-chloro-*trans*-4,5-dimethyl-1,2,3-dioxaphospholane(IV),[3] where one of the methyl groups occurs as a doublet and the other as a double doublet. Mixtures